10/518043

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Description

Diaminopyrimidinecarboxamide Derivative

Technical Field

The present invention relates to medicaments, particularly STAT 6 (signal transducer and activator of transcription 6) inhibitors and novel diaminopyrimidinecarboxamide derivatives useful as agents for treating respiratory diseases in which STAT 6 is participated.

Background of the Invention

It is known that asthma is a disease characterized by a reversible airway obstruction which is accompanied by chronic inflammation and overreaction of airway and that $CD4^+$ T cells, particularly Th2 cell is taking an important role. It is known that Th2 cell is differentiated from Thp cell by IL-4, and that IL-4 and IL-13 produced from Th2 cell cause airway contraction and chronic inflammation of airway through inducing production of IgE antibody production, activation and infiltration of eosinophil and increase of mucus secretion. In addition, it has been reported that IL-13 is also participated in the airway epithelial hypertrophy and airway sub-epithelial fibrosis (*J. Clin. Invest.*, 103, 6, 779 - 788, 1999), destruction of

alveolus (*J. Clin. Invest.*, 106, 1081 - 1093, 2000) and the like symptoms which are found in respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD) and the like.

STAT 6 (signal transducer and activator of transcription 6) is participated in the intracellular signal transduction of IL-4 and IL-13. It has been reported that differentiation of Th2 cell from Thp cell does not occur by the deletion of STAT 6 (*Immunity*, 4, 313 - 319, 1996) and that production of IgE, acceleration of airway reactivity and infiltration of eosinophil into airway and lung are inhibited in an asthma model of STAT 6 deletion mouse (J. Exp. Med., 187, 9, 1537 - 1542, 1998). These reports suggest that STAT 6 participates in inflammatory respiratory diseases such as asthma and the like.

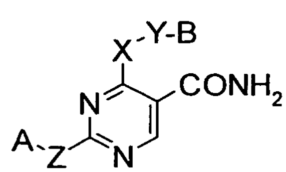
Also, It has been reported that STAT 6 and IL-4 mRNA in nasal mucosa increase by administration of antigens to patients of allergic rhinitis (*Clin. Exp. Allergy*, 30, 86 - 93, 1709 - 1716, 2000) and also that dermatitis-like symptoms such as infiltration of inflammatory cells into the skin are induced by effecting over-expression of IL-4 in mice (*J. Tnvest. Dermatol.*, 117, 4, 977 - 983 (2001)). These reports suggest that STAT 6 participates in allergic rhinitis and dermatitis.

STAT 6 is bonded to GYKXF motif of IL-4 receptor α chain (IL-4Rα) which is a constituting factor of IL-4 receptor and IL-13 receptor (*Science*, 165, 1265 - 1267, 1994), and a JAK family kinase is also bonded to these receptors. When IL-4 or IL-13 is bonded to a receptor, STAT 6 is dimerized by undergoing tyrosine-phosphorylation by the JAK family kinase and translocated into the nucleus where it exerts a function as the transcription factor (*Science*, 165, 1265 - 1267, 1994). Accordingly, if any one of these steps, for example, the tyrosine-phosphorylation of STAT 6, can be inhibited, it becomes possible to inhibit the function of STAT 6 as a transcription factor so that its effectiveness is expected in treating the aforementioned various diseases in which IL-4 and IL-13 are participated.

Since Syk tyrosine kinase as a Zap/Syk family kinase classified into a genealogical relation different from the JAK family kinase based on the gene sequence genealogical tree (Genome Biology, 3, research 0043.1-0043.12) mediates signals from antibody receptors (FcεRI, EcγR) and antigen receptors (BCR, TCR) and apoptosis inhibition signal of eosinophil by GM-CSF, it has been reported that an Syk inhibitor is expected as an agent for inflammations including asthma or allergic diseases (e.g., Patent Reference 1). However, there are no reports on the participation of Syk in the signals of IL-4 and IL-13. It

is considered that an Syk inhibitor expresses its effect by inhibiting all of the activation via respective antigen receptors of B cell and T cell, inhibiting antibody production in the case of antibodies regardless of their subclasses and inhibiting differentiation of helper T cell nonspecifically. That is, it is predicted that Syk inhibitors always accompany inhibitory action of infection protection, immunological functions and the like. In the case of STAT 6 inhibitors on the other hand, since the function of STAT 6 is specific for IL-4 and IL-13, they specifically inhibit production of IgE in the case of antibodies and differentiation of Th2 in the case of T cell subsets. Accordingly, it is expected that STAT 6 inhibitors are effective as agents for treating allergic or inflammatory respiratory diseases having less influences upon infection protection, immunological function and the like (*J. Clin. Inves.*, 109, 1279 - 1283, 2002).

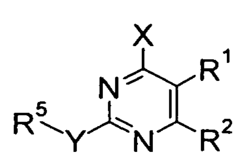
Diaminopyrimidine-5-carboxamide derivatives useful for the treatment of inflammatory and allergic diseases, immune diseases and the like based on the Syk tyrosine kinase inhibition have been reported and, for example, the following compound has been reported in Patent Reference 1.



(Z represents O, NR^2 or a bond and A represents a lower alkyl, aryl or the like which may have a substituent(s), wherein $-NH_2$, -NH-lower alkyl, -N(lower alkyl)$_2$, -NH-lower alkylene-aryl, -NH-cycloalkyl, -NH-aryl, -NH-heteroaryl and the like are disclosed as substituents of said aryl which may have a substituent(s), but they are not a saturated hetero ring, and there is no illustrative disclosure of the 3-chloro-4-hydroxyphenyl group as a substituent of the lower alkyl which may have a substituent. See said published application for details.)

However, there is no disclosure not only on the action of said compound upon STAT 6 but also on its action upon IL-4 and IL-13. Also, since Syk tyrosine kinase concerns itself in the signal transduction of B cell, T cell, mast cell or the like when these cells are stimulated with an antigen, the effect of its inhibitor as an agent for treating inflammatory diseases can be expected, but its immunosuppressive effects and the like must also be taken into consideration.

In addition, compounds having antiviral activities, including diaminopyrimidine-5-carboxamide derivatives, represented by the following general formula have also been reported (e.g., Patent Reference 2).



(X represents $-NR^3R^4$ or the like, Y represents $-N(R^6)-$ or the like, R^1 represents $-C(O)NR^7R^8$ or the like and R^5 represents aryl or the like, and said aryl may be substituted with $-NR'R''$, $-R'$ or the like, wherein said R′ and R″ represent hydrogen, (C1-C8)alkyl, aryl, aryl-(C1-C4)alkyl or aryloxy-(C1-C4)alkyl, but they are not a saturated hetero ring, and there is no disclosure on the illustrative compounds in which the R^5-Y moiety is 4-hydroxyphenetyl group. See said published application for details.)

Also, other pyrimidine-5-carboxamide derivatives useful as PDE 5 inhibitors (e.g., Patent Reference 3; the 2-position substituent of the piperidine ring is a lower alkylamino or indanylamino group which may be substituted), NOS inhibitors (e.g., Patent Reference 4; imidazolylphenyl group and 1,3-benzodioxol-5-yl group are essential), anticancer agents (e.g., Patent Reference 5; the 4-position substituent of the piperidine ring is an amino group which is directly bonded to a ring group), anti-fugal agents (e.g., Patent Reference 6; an alkynyl group is essential on the 4-position substituent of the piperidine ring) and the like have been reported, but all of them do not disclose or suggest on the inhibitory activity for STAT 6 activation.

In addition, dihydrothiadiazole derivatives (e.g., Patent Reference 7), imidazopyrimidine derivatives (e.g., Patent Reference 8), benzofuran derivatives (e.g., Patent

Reference 9), imidazo[2,1-b]thiazole derivatives (e.g., Patent Reference 10), tetrahydroquinoline derivatives (e.g., Patent Reference 11) and the like have been reported as STAT 6 activation inhibitors, but there are no reports on pyrimidine derivatives.

Patent Reference 1

International Publication No. 99/31073 pamphlet

Patent Reference 2

International Publication No. 99/41253 pamphlet

Patent Reference 3

International Publication No. 01/83460 pamphlet

Patent Reference 4

International Publication No. 01/72744 pamphlet

Patent Reference 5

International Publication No. 00/39101 pamphlet

Patent Reference 6

German Patent Application Publication No. 4029650 specification

Patent Reference 7

JP-A-2000-229959

Patent Reference 8

International Publication No. 02/14321 pamphlet

Patent Reference 9

International Publication No. 02/53550 pamphlet

Patent Reference 10

JP-A-11-106340

Patent Reference 11

International Publication No. 02/79165 pamphlet

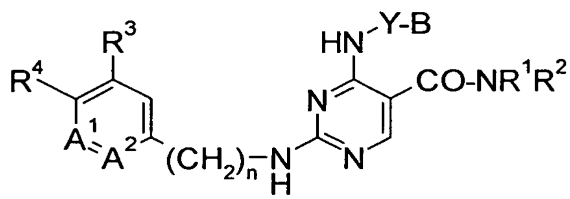
Since inhibitors of STAT 6 activation are expected as agents for treating respiratory diseases such as asthma, COPD and the like, great demand has been directed toward the development of novel compounds.

Disclosure of the Invention

The present inventors have found that diaminopyrimidine-5-carboxamide derivatives partly disclosed in Patent Reference 1 have the inhibitory activity for STAT 6 activation. A compound having said inhibitory activity can be expected as an agent for treating respiratory diseases such as asthma, COPD and the like, having less suppressive effect on immunological function, and also is useful as an agent for treating other inflammatory and allergic diseases. Accordingly, intensive studies on the compounds having the inhibitory activity for STAT 6 activation were conducted, with the aim of providing novel compounds which have less side effects and are useful for the treatment of respiratory diseases and the like and further providing medicaments containing them. As a result, a novel diaminopyrimidine-5-carboxamide derivative having an aromatic ring group linked to the 2-position through a specified linking arm and a substituted amino group on the 4-position was found, and it was found that

said compound has a potent and selective STAT 6 inhibitory activity, thereby accomplishing the present invention.

That is, the present invention relates to a STAT 6 activation inhibitor which comprises a diaminopyrimidinecarboxamide derivative represented by the following formula (I) or a salt thereof as the active ingredient,



(I)

(symbols in the formula have the following meanings:

A^1: CR^5 or N,

R^5: -H, -lower alkyl, -O-lower alkyl or -halogen,

A^2: CR^6 or N,

R^6: -H or -halogen,

R^3: $-R^0$, -lower alkyl substituted with halogen, -halogen, $-OR^0$, -S-lower alkyl, -CO-lower alkyl, $-CO_2$-lower alkyl, -lower alkylene-OH, -hetero ring, -O-hetero ring, $-N(R^0)$-hetero ring, -lower alkylene-hetero ring, -O-lower alkylene-hetero ring, -S-lower alkylene-hetero ring, -SO-lower alkylene-hetero ring, $-SO_2$-lower alkylene-hetero ring, $-N(R^0)$-lower alkylene-hetero ring, -lower alkylene-CO-hetero ring, -lower alkylene-$N(R^0)_2$, $-SO_2-N(R^0)$-lower alkyl or -lower alkylene-$N(R^0)-CO_2$-lower alkylene-phenyl,

R^0: the same or different from one another, and each is H or a lower alkyl,

n: 0 or 2,

R^4: (i) when n = 2, $-R^0$, lower alkyl substituted with halogen, $-OR^0$, $-N(R^0)-CHO$, $-N(R^0)-CO$-lower alkyl or $-N(R^0)-SO_2$-lower alkyl,

(ii) when n = 0, -H, lower alkyl substituted with halogen, -OH, -NH-CHO, $-CON(R^0)_2$, -lower alkylene substituted with halogen-OH, -lower alkylene-NH_2, -lower alkylene-$NHCONH_2$, -lower alkylene-CO_2H, -lower alkylene-CO_2-lower alkyl, -lower alkylene-CN, or -CH(lower alkylene-OH)$_2$, or a group represented by a formula $-X^a-R^{4a}$,

X^a: single bond, -O-, -CO-, -S-, $-SO_2-$, $-N(R^0)-$, $-N(R^0)CO-$, $-N(R^0)SO_2-$, -lower alkylene-O-, -lower alkylene-$N(R^0)$-, -lower alkylene-$N(R^0)CO$-, -lower alkylene-$N(R^0)SO_2$-, -lower alkylene-$N(R^0)CO_2$-, $-N(CO-R^0)-$, $-N(SO_2$-lower alkyl$)-$, $-CON(R^0)-$, -lower alkylene-O-CO-, -lower alkenylene-CO-, -lower alkenylene-$CON(R^0)$-, -lower alkenylene-CO_2-, $-O-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-N(R^0)-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-CO-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-CON(R^0)-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$ or $-N(R^0)CO-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$,

k and m, the same or different from each other, and each is 0, 1, 2, 3 or 4,

R^{4a}: lower alkyl, phenyl, hetero ring, cycloalkyl, lower alkylene-phenyl, lower alkylene-hetero ring, lower

alkylene-OH, lower alkenyl, lower alkenylene-phenyl or lower alkenylene-hetero ring,

wherein the hetero rings in R^3 and R^{4a} may be substituted with 1 to 5 of lower alkyl, halogen, $-OR^0$, -S-lower alkyl, -S(O)-lower alkyl, $-SO_2$-lower alkyl, lower alkylene-OR^0, $-N(R^0)_2$, $-CO_2R^0$, $-CON(R^0)_2$, -CN, -CHO, $-SO_2N(R^0)_2$, $-N(R^0)-SO_2$-lower alkyl, $-N(R^0)-CO-N(R^0)_2$, $-N(R^0)-CO_2$-lower alkyl, $-N(R^0)-CO_2$-cycloalkyl, -NH-C(=NH)-NH-lower alkyl, -NH-C(=N-CN)-NH-lower alkyl, hetero ring (said hetero ring may be substituted with 1 to 5 substituents selected from lower alkyl, OH and lower alkylene-OH), -lower alkylene-NH-C(=NN)-NH_2, -O-phenyl, -CO-phenyl, $-N(R^0)$-CO-lower alkyl, $-N(R^0)$-CO-lower alkylene-$N(R^0)_2$, -lower alkylene-$N(R^0)$-CO-lower alkylene-$N(R^0)_2$, $-CO-N(R^0)$-lower alkylene-$N(R^0)_2$, -CO-lower alkylene-$N(R^0)_2$, -CO-lower alkylene-CO_2R^0, -lower alkylene-$N(R^0)_2$, -lower alkylene-CO_2R^0, -lower alkylene-CO-$N(R^0)_2$, -lower alkylene-$N(R^0)$-CO-lower alkyl, -lower alkylene-$N(R^0)-CO_2$-lower alkyl, -lower alkylene-$N(R^0)-SO_2$-lower alkyl, -lower alkylene-hetero ring (said hetero ring may be substituted with 1 to 5 substituents selected from lower alkyl, OH and lower alkylene-OH), lower alkylene-O-lower alkylene-phenyl, =N-O-R^0 or oxo, and phenyl and cycloalkyl may be substituted with 1 to 5 of lower alkyl, OH, O-lower alkyl or $N(R^0)_2$, and

wherein the lower alkylene in R^3, R^4, R^{4a} and X^a may be substituted with 1 to 5 of $-OR^0$, $-CO_2R^0$, $-CON(R^0)_2$, $-N(R^0)_2$, $-N(R^0)COR^0$ or hetero ring, or

R^3 and R^4 may together form $*-N(R^7)-(CH_2)_2-$, $*-(CH_2)_2-N(R^7)-$, $*-CH_2-N(R^7)-CH_2-$, $*-N(R^7)-(CH_2)_3-$, $*-(CH_2)_3-N(R^7)-$, $*-CH_2-N(R^7)-(CH_2)_2-$, $*-(CH_2)_2-N(R^7)-CH_2-$, $*-C(O)-N(R^7)-(CH_2)_2-$, $*-(CH_2)_2-N(R^7)-C(O)-$, $*-N(R^7)-CH=CH-$, $*-CH=CH-N(R^7)-$, $*-N=CH-CH=CH-$, $*-CH=N-CH=CH-$, $*-CH=CH-N=CH-$, $*-CH=CH-CH=N-$, $*-N=CH-CH=N-$, $*-CH=N-N=CH-$, $*-N(R^7)-N=CH-$, $*-CH=N-N(R^7)-$, $*-O-CH_2-O-$, $*-O-(CH_2)_2-O-$, $*-O-(CH_2)_3-O-$, $*-O-(CH_2)_2-N(R^7)-$, $*-(CH_2)_2-C(O)-$, $*-CH=CH-C(O)-O-$ or $*-N=C(CF_3)-NH-$,

wherein * indicates bonding to the position shown by R^3,

R^7: -H, -lower alkyl or -CO-lower alkyl,

B: H, lower alkenyl, lower alkynyl, lower alkyl substituted with halogen, CN, S-lower alkyl, aryl which may have a substituent(s), cycloalkyl which may have a substituent(s) or hetero ring which may have a substituent(s),

Y: single bond; or lower alkylene which may be substituted with 1 to 5 groups selected from halogen, OH, O-lower alkyl, $-NH_2$, -NH-lower alkyl and -N(lower alkyl)$_2$, and

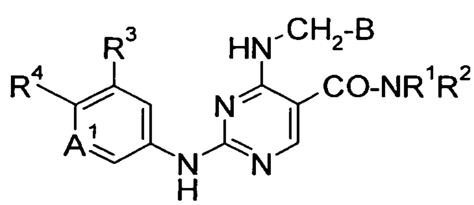
R^1 and R^2: the same or different from each other, and each represents H, lower alkyl or O-lower alkyl which may have a substituent(s)).

Also, according to the present invention, a Th2 cell differentiation inhibitor which comprises a

diaminopyrimidinecarboxamide derivative or a salt thereof as the active ingredient.

Also, the present invention relates to the use of the diaminopyrimidinecarboxamide derivative represented by formula (I) or a salt thereof for the manufacture of a STAT 6 activation inhibitor or a Th2 cell differentiation inhibitor. Also, the present invention relates to a method for inhibiting activation of STAT 6 or a method for inhibiting differentiation of Th2 cell, which comprises administering an effective amount of the diaminopyrimidinecarboxamide derivative represented by formula (I) or a salt thereof to a mammal.

The present invention also relates to a novel diaminopyrimidinecarboxamide derivative represented by the following formula (Ia) or a salt thereof, which is included in the compounds of the aforementioned formula (I), characterized in that it has at least one saturated heterocyclic group in the R^4 of formula (I).



(Ia)

(symbols in the formula have the following meanings:

A^1: CR^5 or N,

R^5: -H, -lower alkyl, -O-lower alkyl or -halogen,

R^3: $-R^0$, -lower alkyl substituted with halogen, -halogen,

$-OR^0$, -S-lower alkyl, -CO-lower alkyl, $-CO_2$-lower alkyl, -lower alkylene-OH, -saturated hetero ring, $-X^b$-heteroaryl, $-X^b$-saturated hetero ring, $-X^b$-heteroaryl, -lower alkylene-$N(R^0)_2$, $-SO_2-N(R^0)$-lower alkyl or -lower alkylene-$N(R^0)-CO_2$-lower alkylene-phenyl,

X^b: -lower alkylene-, -O-lower alkylene-, -S-lower alkylene-, -SO-lower alkylene-, $-SO_2$-lower alkylene-, $-N(R^0)$-lower alkylene- or -lower alkylene-CO-,

R^0: the same or different from one another, and each represents H or a lower alkyl,

R^4: $-X^a$-saturated hetero ring, -lower alkylene-saturated hetero ring or -lower alkenylene-saturated hetero ring,

X^a: single bond, -O-, -CO-, -S-, $-SO_2-$, $-N(R^0)-$, $-N(R^0)CO-$, $-N(R^0)SO_2-$, -lower alkylene-O-, -lower alkylene-$N(R^0)-$, -lower alkylene-$N(R^0)CO-$ or -lower alkylene-$N(R^0)SO_2-$, -lower alkylene-$N(R^0)CO_2-$, $-N(CO-R^0)-$, $-N(SO_2$-lower alkyl$)-$, $-CON(R^0)-$, -lower alkylene-O-CO-, -lower alkenylene-CO-, -lower alkenylene-$CON(R^0)-$, -lower alkenylene-CO_2-, $-O-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-N(R^0)-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-CO-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-CON(R^0)-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$ or $-N(R^0)CO-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$,

k and m: the same or different from each other, and each is 0, 1, 2, 3 or 4,

wherein the saturated hetero rings in R^3 and R^{4a} may be substituted with 1 to 5 of lower alkyl, halogen, $-OR^0$,

-S-lower alkyl, -S(O)-lower alkyl, $-SO_2$-lower alkyl, lower alkylene-OR^0, $-N(R^0)_2$, $-CO_2R^0$, $-CON(R^0)_2$, -CN, -CHO, $-SO_2N(R^0)_2$, $-N(R^0)-SO_2$-lower alkyl, $-N(R^0)-CO-N(R^0)_2$, $-N(R^0)-CO_2$-lower alkyl, $-N(R^0)-CO_2$-cycloalkyl, -NH-C(=NH)-NH-lower alkyl, -NH-C(=N-CN)-NH-lower alkyl, saturated hetero ring (said hetero ring may be substituted with 1 to 5 substituents selected from lower alkyl, OH and lower alkylene-OH), heteroaryl, -lower alkylene-NH-C(=NN)-NH_2, -O-phenyl, -CO-phenyl, $-N(R^0)$-CO-lower alkyl, $-N(R^0)$-CO-lower alkylene-$N(R^0)_2$, -lower alkylene-$N(R^0)$-CO-lower alkylene-$N(R^0)_2$, -CO-$N(R^0)$-lower alkylene-$N(R^0)_2$, -CO-lower alkylene-$N(R^0)_2$, -CO-lower alkylene-CO_2R^0, -lower alkylene-$N(R^0)_2$, -lower alkylene-CO_2R^0, -lower alkylene-CO-$N(R^0)_2$, -lower alkylene-$N(R^0)$-CO-lower alkyl, -lower alkylene-$N(R^0)-CO_2$-lower alkyl, -lower alkylene-$N(R^0)-SO_2$-lower alkyl, -lower alkylene-hetero ring (said hetero ring may be substituted with 1 to 5 substituents selected from lower alkyl, OH and lower alkylene-OH), -lower alkylene-O-lower alkylene-phenyl, $=N-O-R^0$ or oxo, and phenyl and cycloalkyl may be substituted with 1 to 5 of lower alkyl, OH, O-lower alkyl or $N(R^0)_2$, and

wherein the lower alkylene in R^3, R^4 and X^a may be substituted with 1 to 5 of $-OR^0$, $-CO_2R^0$, $-CON(R^0)_2$, $-N(R^0)_2$, $-N(R^0)COR^0$ or hetero ring, or

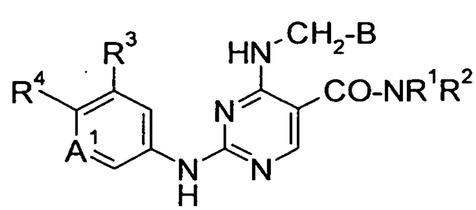
R^3 and R^4 may together form $*-N(R^7)-(CH_2)_2-$, $*-(CH_2)_2-N(R^7)-$, $*-CH_2-N(R^7)-CH_2-$, $*-N(R^7)-(CH_2)_3-$, $*-(CH_2)_3-N(R^7)-$, $*-CH_2-N(R^7)-(CH_2)_2-$, $*-(CH_2)_2-N(R^7)-CH_2-$, $*-C(O)-N(R^7)-(CH_2)_2-$, $*-(CH_2)_2-N(R^7)-C(O)-$, $*-N(R^7)-CH{=}CH-$, $*-CH{=}CH-N(R^7)-$, *-N=CH-CH=CH-, *-CH=N-CH=CH-, *-CH=CH-N=CH-, *-CH=CH-CH=N-, *-N=CH-CH=N-, *-CH=N-N=CH-, $*-N(R^7)-N{=}CH-$, $*-CH{=}N-N(R^7)-$, $*-O-CH_2-O-$, $*-O-(CH_2)_2-O-$, $*-O-(CH_2)_3-O-$, $*-O-(CH_2)_2-N(R^7)-$, $*-(CH_2)_2-C(O)-$, *-CH=CH-C(O)-O- or $*-N{=}C(CF_3)-NH-$, wherein * indicates bonding to the position shown by R^3,

R^7: -H, -lower alkyl or -CO-lower alkyl,

B: aryl which may have a substituent(s) or heteroaryl which may have a substituent(s), and

R^1 and R^2: the same or different from each other, and each represents H, lower alkyl or O-lower alkyl which may have a substituent(s)).

In addition, the present invention also relates to a novel diaminopyrimidinecarboxamide derivative represented by the following formula (Ib) or a pharmaceutically acceptable salt thereof, which is included in the compounds of the aforementioned formula (I), characterized in that it has at least one saturated hetero ring group in the R^3 of formula (I).



(Ib)

(symbols in the formula have the following meanings:

A^1: CR^5 or N,

R^5: -H, -lower alkyl, -O-lower alkyl or -halogen,

R^3: -saturated hetero ring or $-X^b$-saturated hetero ring,

X^b: -lower alkylene-, -O-, $-N(R^0)-$, -O-lower alkylene-, -S-lower alkylene-, -SO-lower alkylene-, $-SO_2$-lower alkylene-, $-N(R^0)$-lower alkylene- or -lower alkylene-CO-,

R^0: the same or different from one another, and each represents H or a lower alkyl,

R^4: -H, -lower alkyl substituted with halogen, -OH, -NH-CHO, $-CON(R^0)_2$, -lower alkylene substituted with halogen-OH, -lower alkylene-NH_2, -lower alkylene-$NHCONH_2$, -lower alkylene-CO_2H, -lower alkylene-CO_2-lower alkyl, -lower alkylene-CN, -CH(lower alkylene-OH)$_2$ or $-X^a-R^{4a}$,

X^a: single bond, -O-, -CO-, -S-, $-SO_2-$, $-N(R^0)-$, $-N(R^0)CO-$, $-N(R^0)SO_2-$, -lower alkylene-O-, -lower alkylene-$N(R^0)-$, -lower alkylene-$N(R^0)CO-$ or -lower alkylene-$N(R^0)SO_2-$, -lower alkylene-$N(R^0)CO_2-$, $-N(CO-R^0)-$, $-N(SO_2$-lower alkyl)-, $-CON(R^0)-$, -lower alkylene-O-CO-, -lower alkenylene-CO-, -lower alkenylene-$CON(R^0)-$, -lower alkenylene-CO_2-, $-O-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-N(R^0)-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-CO-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$, $-CON(R^0)-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$ or $-N(R^0)CO-(CH_2)_k$-cycloalkylene-$(CH_2)_m-$,

k and m: the same or different from each other, and each is 0, 1, 2, 3 or 4,

R^{4a}: lower alkyl, phenyl, heteroaryl, cycloalkyl, lower alkylene-phenyl, lower alkylene-heteroaryl, lower alkylene-OH, lower alkenyl, lower alkenylene-phenyl or lower alkenylene-heteroaryl,

wherein the saturated hetero ring and heteroaryl in R^3 and R^{4a} may be substituted with 1 to 5 of lower alkyl, halogen, $-OR^0$, -S-lower alkyl, -S(O)-lower alkyl, $-SO_2$-lower alkyl, lower alkylene-OR^0, $-N(R^0)_2$, $-CO_2R^0$, $-CON(R^0)_2$, -CN, -CHO, $-SO_2N(R^0)_2$, $-N(R^0)-SO_2$-lower alkyl, $-N(R^0)-CO-N(R^0)_2$, $-N(R^0)-CO_2$-lower alkyl, $-N(R^0)-CO_2$-cycloalkyl, -NH-C(=NH)-NH-lower alkyl, -NH-C(=N-CN)-NH-lower alkyl, hetero ring (said hetero ring may be substituted with 1 to 5 substituents selected from lower alkyl, OH and lower alkylene-OH), -lower alkylene-NH-C(=NN)-NH_2, -O-phenyl, -CO-phenyl, $-N(R^0)$-CO-lower alkyl, $-N(R^0)$-CO-lower alkylene-$N(R^0)_2$, -lower alkylene-$N(R^0)$-CO-lower alkylene-$N(R^0)_2$, -CO-$N(R^0)$-lower alkylene-$N(R^0)_2$, -CO-lower alkylene-$N(R^0)_2$, -CO-lower alkylene-CO_2R^0, -lower alkylene-$N(R^0)_2$, -lower alkylene-CO_2R^0, -lower alkylene-CO-$N(R^0)_2$, -lower alkylene-$N(R^0)$-CO-lower alkyl, -lower alkylene-$N(R^0)-CO_2$-lower alkyl, -lower alkylene-$N(R^0)-SO_2$-lower alkyl, -lower alkylene-hetero ring (said hetero ring may be substituted with 1 to 5 substituents selected from lower alkyl, OH and lower alkylene-OH), -lower alkylene-O-lower alkylene-phenyl, =N-

O-R^0 or oxo, and phenyl and cycloalkyl may be substituted with 1 to 5 of lower alkyl, OH, O-lower alkyl or $N(R^0)_2$, or the lower alkylene in R^3, R^4, R^{4a} and X^a may be substituted with 1 to 5 of -OR^0, -CO_2R^0, -$CON(R^0)_2$, -$N(R^0)_2$, -$N(R^0)COR^0$ or hetero ring, or

R^3 and R^4 may together form *-N(R^7)-(CH_2)$_2$-, *-(CH_2)$_2$-N(R^7)-, *-CH_2-N(R^7)-CH_2-, *-N(R^7)-(CH_2)$_3$-, *-(CH_2)$_3$-N(R^7)-, *-CH_2-N(R^7)-(CH_2)$_2$-, *-(CH_2)$_2$-N(R^7)-CH_2-, *-C(O)-N(R^7)-(CH_2)$_2$-, *-(CH_2)$_2$-N(R^7)-C(O)-, *-N(R^7)-CH=CH-, *-CH=CH-N(R^7)-, *-N=CH-CH=CH-, *-CH=N-CH=CH-, *-CH=CH-N=CH-, *-CH=CH-CH=N-, *-N=CH-CH=N-, *-CH=N-N=CH-, *-N(R^7)-N=CH-, *-CH=N-N(R^7)-, *-O-CH_2-O-, *-O-(CH_2)$_2$-O-, *-O-(CH_2)$_3$-O-, *-O-(CH_2)$_2$-N(R^7)-, *-(CH_2)$_2$-C(O)-, *-CH=CH-C(O)-O- or *-N=C(CF_3)-NH-, wherein * indicates bonding to the position shown by R^3,

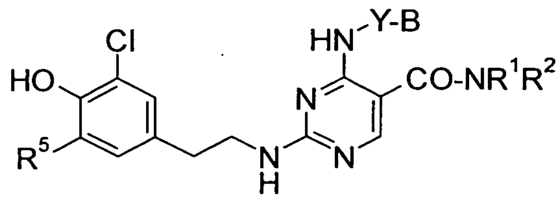
R^7: -H, -lower alkyl or -CO-lower alkyl,

B: aryl which may have a substituent(s) or heteroaryl which may have a substituent(s), and

R^1 and R^2: the same or different from each other, and each represents H, lower alkyl or O-lower alkyl which may have a substituent(s)).

Further, the present invention also relates to a novel diaminopyrimidinecarboxamide derivative represented by the following formula (Ic) or a pharmaceutically acceptable salt thereof, which is included in the compounds of the aforementioned formula (I), characterized in that

the amino group at 2-position is a (substituted phenyl)ethylamino group.



(Ic)

(symbols in the formula have the following meanings:

R^5: -H or -halogen,

B: phenyl which may have 1 to 3 substituents selected from lower alkyl and halogen,

Y: single bond or $-CH_2-$, and

R^1 and R^2: the same or different from each other, and each represents H or lower alkyl which may have a substituent(s)).

Furthermore, the present invention also relates to a medicament which comprises a novel diaminopyrimidinecarboxamide derivative represented by the aforementioned formula (Ia), (Ib) or (Ic) or a pharmaceutically acceptable salt thereof as the active ingredient, particularly a pharmaceutical composition which is effective as a preventive or therapeutic agent for respiratory diseases such as asthma, COPD and the like.

The present invention is described in detail in the following.

The terms "alkyl", "alkenyl", "alkynyl", "alkylene" and "alkenylene" as used herein mean straight chain form or

branched form hydrocarbon chains. The "lower alkyl" is preferably a C_{1-6} alkyl, more preferably a C_{1-4} alkyl, further preferably C_{1-3} alkyl such as methyl, ethyl, isopropyl or the like. The "lower alkylene" is preferably a C_{1-6} alkylene, more preferably a C_{1-4} alkylene, further preferably a C_{1-2} alkylene. The "lower alkenyl" means that it has one or more double bonds at optional positions of a C_{2-6} alkyl, The "lower alkynyl" means that it has one or more triple bonds at optional positions of a C_{2-6} alkyl chain, and the "lower alkenylene" means that it has one or more double bonds at optional positions of a C_{2-6} alkylene.

The "halogen" represents F, Cl, Br and I, preferably F, Cl and Br.

The "lower alkyl substituted with halogen" is a lower alkyl substituted with one or more of halogen, preferably a C_{1-2} alkyl having from 1 to 5 F, and its examples include fluoromethyl, difluoromethyl, trifluoromethyl and trifluoroethyl. The "lower alkylene substituted with halogen" is a lower alkylene substituted with one or more of halogen, preferably a C_{1-3} alkylene having from 1 to 6 F.

Preferred as the "aryl group" is a monocyclic to tricyclic aryl group having from 6 to 14 carbon atoms. More preferred are phenyl and naphthyl groups. In addition, a five- to eight-membered cycloalkyl ring may be fused with phenyl group to form, for example, indanyl, tetrahydronaphthyl or the like. The "cycloalkyl group" is

a cycloalkyl group having from 3 to 12 carbon atoms, and it may form a bridged ring or spiro-ring. Preferred are cycloalkyl groups having from 3 to 10 carbon atoms, and more preferred are cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl and norbornyl.

The "cycloalkylene" means a divalent group formed by removing one hydrogen atom at an optional position of "cycloalkyl group", and its examples include cyclohexane-1,4-diyl, cyclohexane-1,1-diyl, cyclopentane-1,1-diyl and the like.

The "saturated hetero ring" represents a 4- to 8-membered saturated monocyclic hetero ring group containing 1 to 4 hetero atoms selected from O, S and N, and a bicyclic or tricyclic hetero ring group in which said saturated monocyclic hetero rings are fused each other, or a monocyclic hetero ring is fused with a cycloalkyl ring(s). It may form an oxide or dioxide through the oxidation of S or N as a ring atom, or may form a bridged ring or a spiro-ring. Their preferred examples include saturated hetero rings such as piperidyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrazolidinyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl, dioxolanyl, homomorpholinyl and the like, or bridged rings such as 2,5-diazabicyclo[2,2,1]heptyl, 2,8-diazaspiro[4,5]decane and the like.

The "heteroaryl" represents a 5- or 6-membered monocyclic heteroaryl containing 1 to 4 hetero atoms selected from O, S and N, and a bicyclic or tricyclic hetero ring group in which (i) heteroaryl groups each other, (ii) heteroaryl and cycloalkyl ring, (iii) heteroaryl and benzene ring, (iv) saturated hetero ring and heteroaryl or (v) saturated hetero ring and benzene ring are fused. It may form an oxide or dioxide through the oxidation of S or N as a ring atom, or may form a bridged ring or spiro-ring. Preferably, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, imidazolyl, triazolyl, tetrazolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzoimidazolyl, benzothiazolyl, chromanyl, quinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, pyrrolidinyl and the like may be exemplified.

The "hetero ring group" includes the aforementioned "saturated hetero ring" and "heteroaryl" and "partially unsaturated hetero ring" such as dihydropyridyl, dihydropyrrolyl, dihydroxazolyl, dihydrothiazolyl, dihydroimidazolyl, tetrahydropyrimidinyl and the like.

The term "which may have a substituent(s)" means "not substituted" or "substituted with the same or different 1 to 5 substituents".

The substituent in the "cycloalkyl which may have a substituent(s)" is a group which may be used as a substituent of these rings, and is preferably a group selected from the following group G.

Group G: -lower alkyl, -OH, -O-lower alkyl, -aryl, -hetero ring and oxo.

The substituent in the "aryl which may have a substituent" and "hetero ring which may have a substituent(s)" is a group which may be used as a substituent(s) of these rings, and is preferably a group selected from the following group P.

Group P: -lower alkyl which may be substituted with a group of group Q, -lower alkyl substituted with halogen, -halogen, -OH, -CN, -O-(lower alkyl which may be substituted with a group of group Q), -O-lower alkyl substituted with halogen, -S-lower alkyl, $-NH_2$, -NH-(lower alkyl which may be substituted with a group of group Q), -N-(lower alkyl which may be substituted with a group of group $Q)_2$, -CO-lower alkyl, -lower alkylene-OH, -lower alkylene-hetero ring, -lower alkylene-phenyl, -hetero ring, -CO-hetero ring, -CHO, $-CO_2H$, $-CO_2$ lower alkyl, -nitro, -SO-lower alkyl, $-SO_2$ lower alkyl and -NHCO-(lower alkyl which may be substituted with a group of group Q). In this connection, hetero ring and phenyl may be substituted with -lower alkyl, -halogen or -OH.

The substituent in the "lower alkyl which may have a substituent(s)" is a group which may be used as a substituent(s) of these rings, and is preferably a group selected from the following group Q.

Group Q: -OH, -O-lower alkyl, -S-lower alkyl, $-NH_2$, -NH-lower alkyl, -N(lower alkyl)$_2$, $-CO_2H$, $-CONH_2$, -aryl and -hetero ring. In this connection, aryl may be substituted with -lower alkyl, -halogen or -OH, and hetero ring may be substituted with -lower alkyl, -OH or oxo.

Preferred compound among the compound (I) useful as the active ingredient of the present invention is a compound represented by the formula (Ia), formula (Ib) or formula (Ic), and in the other preferred embodiment, R^3 and R^4 together form $*-N(R^7)-(CH_2)_2-$, $*-(CH_2)_2-N(R^7)-$, $*-N(R^7)-(CH_2)_3-$, $*-(CH_2)_3-N(R^7)-$, $*-CH_2-N(R^7)-(CH_2)_2-$ or $*-(CH_2)_2-N(R^7)-CH_2-$. In this case, preferred as R^7 is H, methyl or acetyl.

Preferred embodiment of the compound (Ia) is shown in the following:

A^1 is preferably CH, C-halogen, C-(O-lower alkyl) or N, more preferably CH, C-halogen or C-(O-lower alkyl), further preferably CH or C-halogen, most preferably CH.

R^3 is preferably $-R^0$, -lower alkyl substituted with halogen, -halogen, $-OR^0$, -saturated hetero ring, -lower alkylene-heteroaryl or -lower alkylene-saturated hetero ring, more preferably -H, -halogen, -OH, $-O-C_{1-3}$ alkyl or

-lower alkylene-saturated hetero ring, further preferably -H, -Cl, -F or -Br, wherein said saturated hetero ring may be substituted with 1 to 5 of lower alkyl, OH, O-lower alkyl or oxo.

R^4 is preferably $-X^a$-saturated hetero ring;

wherein X^a is preferably single bond, -O-, -CO-, -S-, $-SO_2-$, $-N(R^0)-$, $-N(R^0)CO-$, -lower alkylene-O-, -lower alkylene-$N(R^0)$- or -lower alkylene-$N(R^0)CO$-, more preferably single bond, -O-, -CO-, -S-, $-N(R^0)-$, $-N(R^0)CO-$ or -lower alkylene-$N(R^0)CO$-;

more preferred is -O-piperidyl, -O-pyrrolidyl, -O-quinuclidinyl, -O-tetrahydrofuranyl, -O-tetrahydropyranyl, -CO-morphorinyl, -CO-piperidyl, -CO-piperazinyl, -S-tetrahydrofuranyl, $-SO_2$-piperidyl, $-SO_2$-piperazinyl, $-C_{1-4}$ alkylene-N(Me)-piperidyl, $-C_{1-4}$ alkylene-N(Me)-tetrahydropyranyl, $-C_{1-4}$ alkylene-pyrrolidyl, $-C_{1-4}$ alkylene-piperidyl, $-C_{1-4}$ alkylene-piperazinyl, $-C_{1-4}$ alkylene-morpholinyl, $-C_{1-4}$ alkylene-thiomorpholinyl, $-O-C_{1-4}$ alkylene-pyrrolidyl, $-O-C_{1-4}$ alkylene-piperidyl, $-O-C_{1-4}$ alkylene-piperazinyl, $-O-C_{1-4}$ alkylene-morpholinyl, $-O-C_{1-4}$ alkylene-thiomorpholinyl, -piperidyl, -morpholinyl, -thiomorpholinyl, homomorpholinyl, 2,5-diazabicyclo[2,2,1]heptyl, -piperazinyl or homopiperazinyl. In this case, ethylene or dimethylethylene is particularly desirable as the C_{1-4} alkylene. In addition, the aforementioned hetero ring including piperidyl,

piperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, pyrrolidyl, tetrahydrofuranyl and tetrahydropyranyl may be substituted with lower alkyl, OH, O-lower alkyl, -CO-lower alkylene-N(lower alkyl)$_2$, lower alkylene-NHCO-lower alkylene-N(lower alkyl)$_2$, -lower alkylene-N(lower alkyl)$_2$, lower alkylene-CO_2H, -CO_2H, lower alkylene-CO_2-lower alkyl, -CO_2-lower alkyl, lower alkylene-$CONH_2$, -$CONH_2$, lower alkylene-$HNCONH_2$, lower alkylene-NH-SO_2 lower alkyl, lower alkylene-N(lower alkyl)-SO_2 lower alkyl, -lower alkylene-OH or oxo.

B is preferably phenyl, indolyl, indazolyl, furyl or thienyl, and said phenyl, indolyl, indazolyl, furyl and thienyl may have a substituent(s) selected from the aforementioned group P.

Regarding R^1 and R^2, preferred is a case in which R^1 is H and R^2 is H or lower alkyl which may have a substituent(s) selected from the aforementioned group Q, more preferred is a case in which both of R^1 and R^2 are H.

Accordingly, as the compound (Ia), a compound consisting of a combination of the aforementioned preferred groups is more desirable.

Preferred embodiment of the compound (Ib) is shown in the following:

A^1 is preferably CH, C-halogen, C-(O-lower alkyl) or N. More preferably CH or C-halogen, and most preferably CH.

R^3 is preferably -saturated hetero ring, -O-saturated hetero ring, $-N(R^0)$-saturated hetero ring or -lower alkylene-saturated hetero ring, more preferably -lower alkylene-saturated hetero ring including nitrogen atom, wherein said saturated hetero ring including nitrogen atom may be unsubstituted or substituted with 1 to 5 of lower alkyl, OH, O-lower alkyl or oxo.

R^4 is preferably -H, -OH, -NH-CHO, $-CON(R^0)_2$, -lower alkylene substituted with halogen-OH, -lower alkylene-NH_2, -lower alkylene-$NHCONH_2$, -lower alkylene-CO_2H, -lower alkylene-CO_2-lower alkyl, -lower alkylene-CN, or -CH(lower alkylene-OH)$_2$, or a group represented by a formula $-X^a-R^{4a}$,

wherein preferred as X^a is single bond, -O-, -CO-, -S-, $-SO_2-$, $-N(R^0)-$, $-N(R^0)CO-$, -lower alkylene-O-, -lower alkylene-$N(R^0)$- or -lower alkylene-$N(R^0)CO$-, and more preferred is single bond, -O-, -CO-, $-N(R^0)-$, $-N(R^0)CO-$ or -lower alkylene-$N(R^0)CO$-;

more preferred is -OH, $-CON(R^0)_2$, -lower alkylene substituted with halogen-OH, -lower alkylene-CN or -CH(lower alkylene-OH)$_2$, or a group represented by a formula $-X^a-R^{4a}$, further preferred is -CH(lower alkylene-OH)$_2$ or a group represented by the formula $-X^a-R^{4a}$ and most preferred is -OH, $-C_{1-4}$ alkylene-OH, $-CH_2N(Me)_2$, $-C_{1-4}$ alkylene-N(Me)-C_{5-6} cycloalkyl or $-CH(CH_2OH)_2$. In this case, ethylene or dimethylethylene is particularly desirable as the C_{1-4} alkylene. In addition, the aforementioned

cycloalkyl may be substituted with lower alkyl, OH, O-lower alkyl or -N(lower alkyl)$_2$.

B is preferably phenyl, indolyl, indazolyl, furyl or thienyl, and said phenyl, indolyl, indazolyl, furyl and thienyl may have a substituent selected from the aforementioned group P.

Regarding R^1 and R^2, preferred is a case in which R^1 is H and R^2 is H or lower alkyl which may have a substituent selected from the aforementioned group Q, more preferred is a case in which both of R^1 and R^2 are H.

Accordingly, as the compound (Ib), a compound consisting of a combination of the aforementioned preferred groups is more desirable.

Preferred embodiment of the compound (Ic) is shown in the following:

R^5 is preferably -H, -Cl, -F or -Br, more preferably -H or -Cl.

B is preferably H, C_{1-6} alkyl substituted with halogen, aryl which may have a substituent(s), cycloalkyl which may have a substituent(s) or hetero ring which may have a substituent(s), more preferably phenyl, C_{3-8} cycloalkyl, indolyl, indazolyl, furyl, thienyl, adamantyl, norbornyl or tetrahydrofuranyl, and said phenyl, indolyl, indazolyl, furyl and thienyl may have a substituent(s) selected from the aforementioned group P, and the C_{3-8}

cycloalkyl may have a substituent(s) selected from the aforementioned group G.

Y is preferably single bond, or a lower alkylene group which may be substituted with OH or O-C_{1-2} alkyl, more preferably single bond or a C_{1-6} alkylene group. Further preferred is single bond, methylene, methylmethylene or ethylene. Alternatively, in case that B is H, preferred as Y-B is 2-propyl, 2-methylpropyl, tert-butyl, 2,2-dimethylpropyl or 3-methylbutyl.

Preferable R^1 and R^2 include those in which R^1 is H and R^2 is H or lower alkyl which may have a substituent(s) selected from the aforementioned group Q, more preferably, those in which both of R^1 and R^2 are H.

Accordingly, as the compound (Ic), a compound consisting of a combination of the aforementioned preferred groups is more desirable.

Particularly desirable compounds regarding the compound (I) are the following compounds: 4-benzylamino-2-[(4-morpholin-4-ylphenyl)amino]pyrimidine-5-carboxamide, 2-[(4-morpholin-4-ylphenyl)amino]-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide, 4-[(2,6-difluorobenzyl)amino]-2-[(4-morpholin-4-ylphenyl)amino]pyrimidine-5-carboxamide, 4-[(2,5-difluorobenzyl)amino]-2-[(4-morpholin-4-ylphenyl)amino]pyrimidine-5-carboxamide, 4-[(2-methoxybenzyl)amino]-2-[(4-morpholin-4-

ylphenyl)amino]pyrimidine-5-carboxamide, 4-[(2-fluoro-6-methoxybenzyl)amino]-2-[(4-morpholin-4-ylphenyl)amino]pyrimidine-5-carboxamide, 2-({4-[(1-methylpiperidin-3-yl)oxy]phenyl}amino)-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide, 2-{[4-(1-azabicyclo[2.2.2]oct-3-yloxy)phenyl]amino}-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide, 2-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)amino]-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide, 2-({4-[4-(2-amino-2-oxoethyl)piperazin-1-yl]phenyl}amino)-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide, 2-{[4-(2-morpholin-4-ylethoxy)phenyl]amino}-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide, 2-{[4-(β-D-glucopyranosyloxy)phenyl]amino}-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide, 4-benzylamino-2-{[2-(3-chloro-4-hydroxyphenyl)ethyl]amino}pyrimidine-5-carboxamide, 4-benzylamino-2-{[2-(3,5-dichloro-4-hydroxyphenyl)ethyl]amino}pyrimidine-5-carboxamide, 2-[(4-morpholin-4-ylphenyl)amino]-4-[(2-thienylmethyl)amino]pyrimidine-5-carboxamide, 4-{[(3-chloro-2-thienyl)methyl]amino}-2-[(4-morpholin-4-ylphenyl)amino]pyrimidine-5-carboxamide and 2-{[3-(2-morpholin-4-ylethyl)phenyl]amino}-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide.

The compound (I) and novel compounds (Ia), (Ib) and (Ic) ("compound (I)" hereinafter) useful as the active ingredient of the present invention may exist in the form of geometrical isomers and tautomers depending on the kind of substituents, and their separated forms or mixtures are also included in the present invention. Also, since the compound (I) has asymmetric carbon atom in some cases, isomers based on the asymmetric carbon atom may be present. Mixtures and isolated forms of these optical isomers are included in the present invention. In addition, compounds prepared by labeling the compound (I) with radioisotopes are included in the present invention.

In some cases, the compound (I) forms an acid addition salt or, depending on the kind of substituents, a salt with a base, and such salts are included in the present invention with the proviso that they are pharmaceutically acceptable salts. Their illustrative examples include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like and with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, aspartic acid, glutamic acid and the like, salts with inorganic bases such as sodium, potassium,

magnesium, calcium, aluminum and the like or with organic bases such as methylamine, ethylamine, ethanolamine, lysine, ornithine and the like, ammonium salts and the like. Further, the present invention also includes various hydrates, solvates and polymorphic substances of the compound (I) and its pharmaceutically acceptable salts.

In addition, a pharmacologically acceptable prodrug is also included in the present invention. The pharmacologically acceptable prodrug is a compound having the group of the present invention which may be converted into NH_2, OH, CO_2H or the like by solvolysis or under physiological conditions. As the groups which can form prodrugs, the groups described in *Prog. Med.*, 5, 2157 - 2161 (1985) and "Iyakuhin-no Kaihatsu (Development of Medicaments)" (written in Japanese, Hirokawa Shoten) vol. 7 Bunshi Sekkei (Molecular Design) 163 - 198 may be exemplified.

(Production Methods)

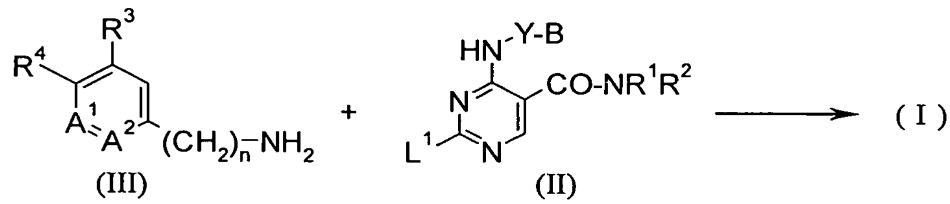
The compound (I) or a pharmaceutically acceptable salt thereof may be produced by employing various conventionally known synthesis methods, making use of the characteristics based on its basic skeleton or the kind of substituents. In that case, depending on the kind of functional group, there is a case in which it is effective from a production technical point of view to protect said

functional group or replace it by a group which may be easily converted into said functional group at a stage of the material or an intermediate. Examples of such a functional group include amino group, hydroxyl group, carboxyl group and the like, examples of their protecting groups include the protecting groups described in "Protective Groups in Organic Synthesis (3rd edition, 1999)" edited by Greene (T.W. Greene) and Wuts (P.G.M. Wuts), and these may be optionally selected and used in response to the reaction conditions. In such a method, a desired compound may be obtained by introducing said protecting group and carrying out the reaction, and then removing the protecting group as occasion demands, or converting it into a desired group. In addition, a prodrug of the compound (I) may be produced by introducing a specified group at a stage of the material or an intermediate similar to the case of the aforementioned protecting group, or carrying out a reaction using the obtained compound (I). The reaction may be carried out by employing a conventional method known to those skilled in the art such as general esterification, amidation, carbamation, dehydration or the like.

The following describes typical production methods of the compounds of the present invention regarding the compound of formula (I), and the compounds of formulae

(Ia), (Ib) and (Ic) can also be produced in the same manner.

Production Method A   Substitution reaction (1)



(In the formula, L^1 represents a leaving group. The same shall apply hereinafter.)

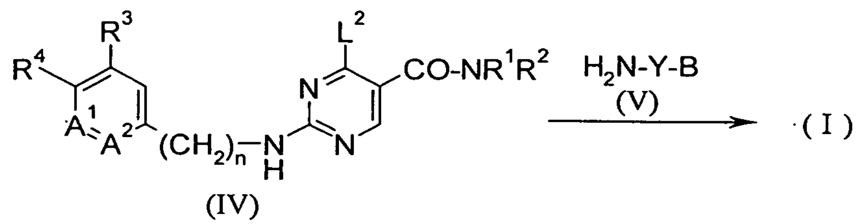
This production method is a method in which the compound (I) is obtained by allowing a pyrimidine compound (II) to react with an amine compound (III). In this case, examples of the leaving group of L^1 include a halogen atom, methylsufanyl, methylsulfinyl, methylsulfonyl, *1H*-benzotriazol-1-yloxy, methylsulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy and the like.

The reaction may be carried out without solvent or in a solvent inert to the reaction such as aromatic hydrocarbon (e.g., benzene, toluene, xylene or the like), ether (e.g., diethyl ether, tetrahydrofuran (THF), dioxane or the like), halogenated hydrocarbon (e.g., dichloromethane, 1,2-dichloroethane, chloroform or the like), N,N-dimethylformamide (DMF), dimethylacetamide (DMA), N-methylpyrrolidone (NMP), ethyl acetate,

acetonitrile or the like, using the compounds (II) and (III) in equimolar basis or one of them in an excess amount, and at room temperature to under heat reflux. The reaction temperature may be optionally set in accordance with the compounds. Depending on the compounds, it is sometimes advantageous to carry out the reaction in the presence of an organic base (preferably diisopropylethylamine, N-methylmorpholine, pyridine or 4-(N,N-dimethylamino)pyridine) or a metal base (preferably potassium carbonate or sodium hydroxide). Also, depending on the compounds, it is sometimes advantageous to carry out the reaction under an acidic condition (in the presence of 4 M hydrogen chloride/1,4-dioxane solution, 4 M hydrogen chloride/ethyl acetate solution or the like) or in the presence of a fluoride ion (potassium fluoride, cesium fluoride, tetrabutylammonium fluoride or the like).

In this connection, in case that the compound (I) has a primary or secondary amino group, it may be produced by protecting amino groups of the compound (II) and compound (III) as the material compounds in advance with a protecting group, carrying out said substitution reaction and then removing the protecting group. The protecting group may be optionally selected from the protecting groups described in the aforementioned "Protective Groups in Organic Synthesis".

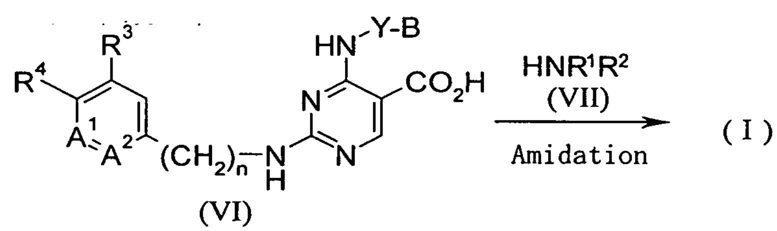
Production Method B Substitution reaction (2)



(In the formula, L^2 represents a leaving group. The same shall apply hereinafter.)

This production method is a method in which the compound (I) is obtained by allowing a pyrimidine compound (IV) to react with an amine compound (V), and it may be produced in the same manner as the method described in the aforementioned Production Method A. In this case, a group similar to the aforementioned leaving group L^1 may be used as the leaving group L^2.

Production Method C Amidation reaction



This production method is a method in which the compound (I) is obtained through the amidation of a carboxylic acid derivative (VI).

A free carboxylic acid or a reactive derivative thereof may be used in this reaction as the carboxylic acid

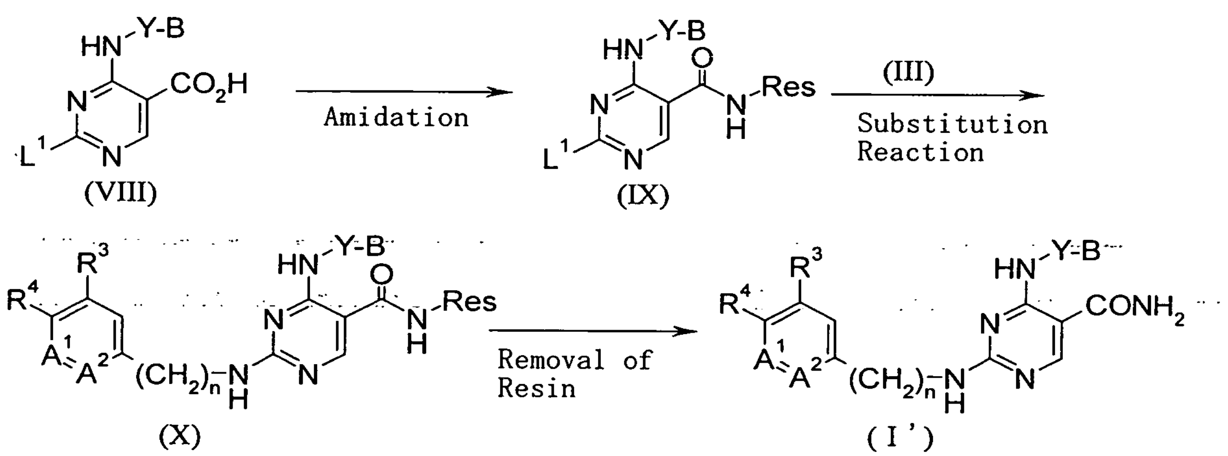
derivative (VI), and examples of said reactive derivative include acid halides (acid chloride, acid bromide and the like), acid anhydrides (mixed anhydride obtained by the reaction with ethyl chlorocarbonate, benzyl chlorocarbonate, phenyl chlorocarbonate, p-toluenesulfonic acid, isovaleric acid and the like, or symmetric acid anhydrides), activated esters (esters which may be prepared using phenol, 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HONSu) or the like that may be substituted with an electron withdrawing group such as a nitro group, a fluorine atom or the like), a lower alkyl ester, an acid azide and the like. These reactive derivatives may be produced in the usual way.

When a free carboxylic acid is used, it is desirable to use a condensing agent (such as (N,N′-dicyclohexylcarbodiimide (DCC), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (WSC), 1,1′-carbonylbisimidazole (CDI), N,N′-disuccinimidyl carbonate, Bop reagent (Aldrich, USA), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), diphenyl phosphate azide (DPPA), phosphorus oxychloride, phosphorus trichloride, triphenylphosphine/N-bromosuccinimide or the like), further using an additive agent (e.g., HONSu, HOBt or the like) as occasion demands.

The reaction is carried out using the carboxylic acid derivative (VI) and an amine (VII) in equimolar basis or

one of them in an excess amount, in an inert solvent such as an aromatic hydrocarbon, a halogenated hydrocarbon, an ether, DMF, DMA, NMP, ethyl acetate, acetonitrile or the like, under cooling to heating, preferably from -20°C to 60°C. Depending on the kind of reactive derivatives, it is sometimes advantageous in effecting smooth progress of the reaction to carry out the reaction in the presence of a base (preferably triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine or the like). Pyridine can also serve as the solvent.

Production Method D   Solid phase synthesis



(In the formula, Res represents a resin for solid phase synthesis. The same shall apply hereinafter.)

This production method is a method producing by a solid phase synthesis method which consists of the following three steps.

(1) Fixation to a resin (amidation)

A carboxylic acid compound (VIII) and a resin for solid phase synthesis use having amino termini (e.g., an amino(methyl) resin, Rink amide resin or the like) are condensed in the same manner as in the aforementioned Production Method C.

(2) Substitution reaction

The production is effected by carrying out a substitution reaction in the same manner as in Production Method A using the amine compound (III).

(3) Removal of the resin

A compound (I′) is produced by eliminating the resin from a compound (X). The reaction is carried out without solvent or in a solvent inert to the reaction (e.g., an aromatic hydrocarbon, an ether, a halogenated hydrocarbon, an alcohol, DMF, DMA, NMP, pyridine, dimethyl sulfoxide (DMSO), ethyl acetate, acetonitrile or the like), by treating with a mineral acid (e.g., hydrochloric acid, hydrobromic acid or the like) or an organic acid (e.g., trifluoroacetic acid or the like). It is advantageous in some cases to catty out the reaction in the presence of additive agent (e.g., difluoroethanol, triethylsilane, triisopropylsilane, (thio)anisole or the like).

Production Method E Other production methods

The compounds of the present invention having various functional groups such as amido group, ureido group, alkylamino group and the like can also be produced by using the compounds of the present invention having corresponding amino group and the like as the materials and employing a method obvious to those skilled in the art, a conventionally known production method or a modified method thereof. For example, the following reactions may be employed.

E-1: Amidation

Various amide compounds may be produced by allowing various carboxylic acid compounds or reactive derivatives thereof to react with a compound of the present invention having amino group. The aforementioned method Production Method C may be employed in this reaction. In addition, various sulfonamide derivatives may be produced by the use of various sulfonic acid derivatives (reactive derivatives such as sulfonic acid halides, sulfonic acid anhydrides and the like are desirable) instead of the carboxylic acid compounds.

E-2: Ureation

They may be produced by allowing ureation agents such as a cyanic acid derivative (e.g., sodium cyanate, potassium cyanate or the like), an isocyanate derivative, urea, cyanogen bromide and the like to react with the

compounds of the present invention having amino group, without solvent or in an solvent inert to the reaction (e.g., an aromatic hydrocarbon, an ether, a halogenated hydrocarbon, an alcohol, water, DMF, DMA, NMP, pyridine, DMSO, ethyl acetate, acetonitrile or the like). These solvents may be used alone or as a mixture of two or more. It is sometimes advantageous in effecting smooth progress of the reaction to carry out the reaction in the presence of an acid (e.g., acetic acid, hydrochloric acid or the like) or a base (e.g., sodium hydroxide, potassium hydroxide or the like). The reaction may be carried out under cooling to heating reflux, and the reaction temperature may be optionally set depending on the compound.

E-3: Alkylation (1)

Alkyl groups may be introduced by allowing compounds having amino group to react with various alkylating agents (e.g., alkyl halides, alkyl sulfonic acid esters and the like) in the usual way. In addition, in case that a secondary amine is produced from a primary amine, a method in which a material is once made into a trifluoroacetylamino form, alkylated and then hydrolyzed (*Tetrahedron Letters*, 1978, 4987 and the like) may be employed.

E-4 Alkylation (2)

Alkylated compounds may be produced by subjecting compounds having amino group to a reductive alkylation with various carbonyl compounds. The reaction may be carried out by employing a method described, for example, in "Jikken Kagaku Koza (Experimental Chemistry Course) (Maruzen)" edited by The Chemical Society of Japan (4th edition, vol. 20, 1992, 300).

E-5: Oxidation

Oxide compounds may be obtained by treating compounds having tertiary amino groups or nitrogen-containing aromatic rings (e.g., pyridine and the like) with various oxidizing agents. The reaction may be carried out by employing a method described, for example, in "Jikken Kagaku Koza (Maruzen)" edited by The Chemical Society of Japan (4th edition, vol. 23, 1991, 271).

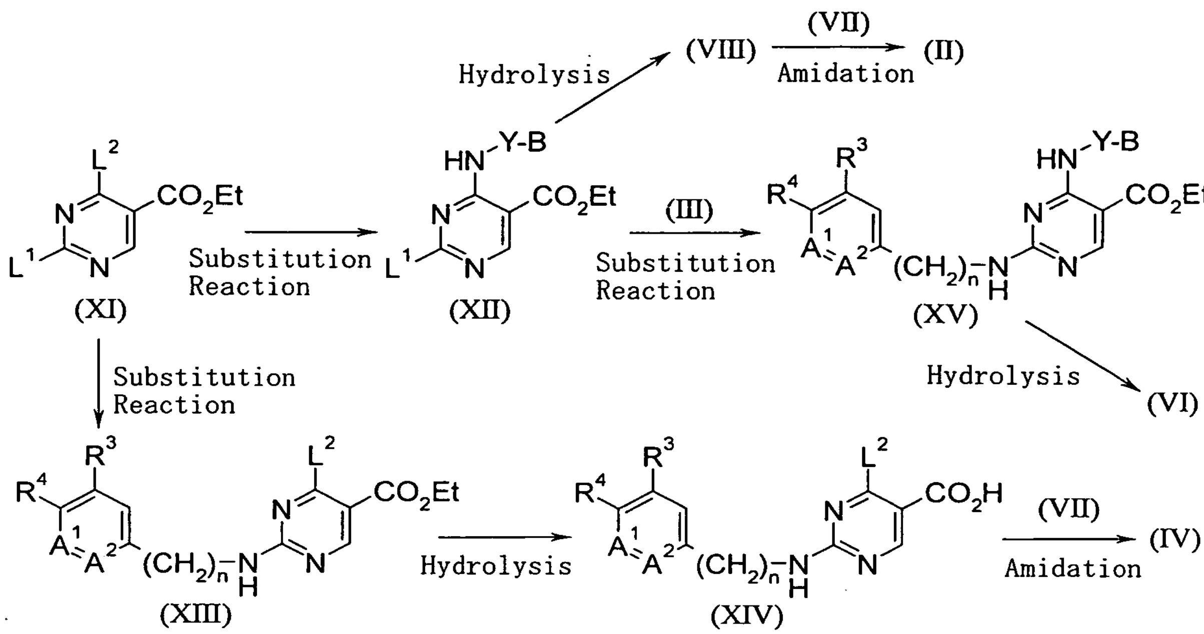
E-6: Reduction

A compound having amino group may be produced by subjecting a compound having oxidoamino group to a reductive treatment (e.g., reaction with sodium hydrogen sulfite or the like).

Production Method F Production method of material compounds

Material compounds to be used in the production of the compound (I) may be produced in the usual way, for

example, using conventionally known reactions shown in the following synthesis pathway.



In the above reaction scheme, the substitution reaction may be carried out in the same manner as in the aforementioned Production Method A or B, and the amidation in the same manner as in the aforementioned Production Method C, respectively. The carboxyl group deprotection condition described in the aforementioned "Protective Groups in Organic Synthesis" may be applied to the hydrolysis, and other alkyl ester, benzyl ester and the like can also be used instead of the ethyl ester.

The reaction products obtained by the aforementioned respective production methods may be isolated and purified as free compounds, salts thereof or various solvates such

as hydrate and the like. The salts may be produced by subjecting to general salt forming treatments.

Isolation and purification may be carried out by employing general chemical operations such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, various types of chromatography and the like.

Various types of isomers may be isolated in the usual way making use of a physicochemical difference between isomers. For example, optical isomers may be separated by a general optical resolution method such as fractional crystallization or chromatography. In addition, optical isomers can also be produced from an appropriate optically active material compound.

Industrial Applicability

As is also confirmed by the following Examples, the compound (I) useful as the active ingredient of the present invention has superior inhibitory activity for STAT 6 activation and is useful as an agent for preventing or treating respiratory diseases (asthma, CODP and the like) and allergic diseases (rhinitis, dermatitis and the like), in which STAT 6 is concerned.

In addition, since the compound (I) has the potent inhibitory activity for STAT 6 activation in comparison with the inhibitory activity for immunocyte activation by

an antigen receptor stimulation and have compounds having a selectivity of 100 times or more, it is useful as the aforementioned preventive or therapeutic agent having less action upon the immunosuppression function. In this connection, the immunocyte activation inhibition by an antigen receptor stimulation may be evaluated, for example, based on the inhibition of intracellular calcium concentration increase in a B cell strain (RAMOS cell) by anti-IgM antibody stimulation and the inhibition of IL-2 production from a mouse spleen-derived T cell by anti-CD3 antibody stimulation.

The pharmaceutical preparation which contains one or two or more of the compounds (I) or salts thereof as the active ingredient is prepared using a carrier, a filler and other additives generally used in preparing medicaments.

Its administration may be in the form of either oral administration through tablets, pills, capsules, granules, powders, solutions and the like, or parenteral administration through injections such as intravenous injections, intramuscular injections or the like, suppositories, percutaneous preparations, transnasal preparations, inhalations and the like. The dose is optionally decided in response to each case, by taking into consideration symptoms, age, sex and the like of each subject to be administered, but is generally from 0.001 mg/kg to 100 mg/kg per day per adult in the case of oral

administration, and this is administered once a day or by dividing into 2 to 4 daily doses, or is within the range of from 0.0001 mg/kg to 10 mg/kg per day per adult in the case of intravenous injection and this is administered once a day or dividing into two or more daily doses. In addition, in the case of transnasal administration, this is administered generally within the range of from 0.0001 mg/kg to 10 mg/kg per day per adult, once a day or dividing into two or more daily doses, and in the case of inhalation, this is administered generally within the range of from 0.0001 mg/kg to 1 mg/kg per day per adult, once a day or dividing into two or more daily doses.

As a solid composition of the present invention for oral administration, tablets, powders, granules and the like are used. In such a solid composition, one or more active substances are mixed with at least one inert excipient such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, aluminum magnesium silicate or the like. In the usual way, this composition may contain inactive additives such as a lubricant (e.g., magnesium stearate or the like), a disintegrating agent (e.g., carboxymethylstarch sodium or the like), and a solubilization assisting agent. As occasion demands, tablets or pills may be coated with a sugar coating or a film of a gastric or enteric coating agent.

The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contains a generally used inert solvent such as purified water or ethanol. In addition to the inert solvent, this composition may contain auxiliary agents such as a solubilizing agent, a moistening agent and a suspending agent, as well as a sweetener, a correctives, an aromatic or an antiseptic.

The injections for parenteral administration includes aseptic aqueous or non-aqueous solutions, suspensions and emulsions. The aqueous solvent includes, for example, distilled water for injection and physiological saline. The non-aqueous solvent includes, for example, propylene glycol, polyethylene glycol, plant oil (e.g., olive oil or the like), alcohol (e.g., ethanol or the like), polysorbate 80 (trade name) and the like. Such a composition may further contain a tonicity agent, an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizing agent, a solubilization assisting agent and the like. These are sterilized, for example, by filtration through a bacteria retaining filter, blending of a germicide or irradiation. Alternatively, a sterile solid composition is produced, which may be used by dissolving or suspending in sterile water or other sterile solvent for injection prior to its use.

In the case of inhalations and transmucosal preparations such as transnasal preparations, those in the solid, liquid or semi-solid state are used, and they may be produced in accordance with conventionally known methods. For example, excipients (e.g., lactose, starch and the like), and also a pH adjusting agent, an antiseptic, a surfactant, a lubricant, a stabilizer, a thickener and the like, may be optionally added. An appropriate device for inhalation and exhalation may be used for the administration. For example, using a conventionally known device or sprayer such as a measuring administration inhalation device, a compound may be administered alone or as a powder of a prescribed mixture, or as a solution or suspension in combination with a pharmaceutically acceptable carrier. A dry powder inhalation device or the like may be for a single or multiple administration use, and a dry powder or powder-containing capsules may be used. Alternatively, it may be a pressure aerosol sprayer type or the like which uses an appropriate propellant such as chlorofluoroalkane, hydrofluoroalkane or carbon dioxide or the like appropriate gas.

Best Mode for Carrying Out the Invention

The following illustratively describes the present invention based on Examples, but these do not limit the scope of the present invention. Production methods of the

material compounds are shown in Reference Examples. In addition, production methods of compounds which are included in the formula (I) but not included in the formula (Ia), (Ib) or (Ic) are shown in Production Examples.

The following abbreviations are used in the Reference Examples and the tables which are shown later. Rex: reference example number, Pre: production example number, Ex: example number, Cmpd: compound number, Str: structural formula, Syn: production method (the figures show example or production example numbers produced in the same manner), Me: methyl, Et: ethyl, Pr: 1-propyl, iPr: 2-propyl, Bu: butyl, tBu: tert-butyl, Boc: tBu-O-CO-, Ac: acetyl, Ms, Me-SO_2-, Ph: phenyl, Bn: benzyl, Bz: benzoyl, cPr: cyclopropyl, cBu: cyclobutyl, cPen: cyclopentyl, cHex: cyclohexyl, cHep: cycloheptyl, cOct: cyclooctyl, 2Ad: 2-adamantyl, 2Py: 2-pyridyl, 3Py: 3-pyridyl, 4Py: 4-pyridyl, 3Qui: 3-quinolyl, Dat: physicochemical date(F: FAB-MS $(M + H)^+$; FN: FAB-MS $(M - H)^-$; ESI: ESI-MS $(M + H)^+$; EI: EI-MS $(M + H)^+$; NMR1: δ (ppm) of characteristic peak of ^1H NMR in DMSO-d_6; NMR2: δ (ppm) of characteristic peak of ^1H NMR in $CDCl_3$; MP: melting point (°C); Sal: salt (no description: free; HCl: hydrochloride; the numeral shows the ratio of acid components, for example, 2HCl means dihydrochloride)). In addition, the number before each substituent indicates the substituting position, and the presence of two or more numbers indicates two or more substitutions. For example,

2-MeO-Ph indicates 2-methoxyphenyl, and 2,4-F_2-Ph indicates 2,4-difluorophenyl.

Reference Example 1

A Boc compound obtained by allowing 4-(2-aminoethyl)aniline to react with tert-butyl dicarbonate in THF was allowed to react with formic acid in dichloromethane in the presence of WSC hydrochloride, thereby obtaining a formylaminophenyl compound. This was further treated with 4 M hydrogen chloride/ethyl acetate solution in ethyl acetate to obtain 4-(2-aminoethyl)phenylformamide hydrochloride. F: 165.

Reference Example 2

3-(2-morpholin-4-ylethyl)aniline was obtained by treating 3-(2-morpholin-4-yl-2-oxoethyl)aniline with lithium aluminum hydride in THF. F: 207.

Reference Example 3

A compound obtained by allowing 4-nitrobenzyl bromide and 2-(morpholin-4-yl)ethylamine to undergo the reaction in DMF in the presence of potassium carbonate was allowed to react with di-tert-butyl carbonate in 1,4-dioxane, thereby obtaining a Boc compound. This was further subjected to catalytic hydrogenation in methanol in the presence of 10%

palladium/carbon to obtain tert-butyl 4-aminobenzyl-(2-morpholin-4-ylethyl)carbamate. F: 336.

Reference Example 4

In the presence of triethylamine, a toluene solution of 2-(4-nitrophenyl)propionic acid was allowed to react with DPPA at room temperature and then under heating, and further allowed to react with tert-butanol under heating, thereby obtaining a Boc compound (F: 366). The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain tert-butyl 1-(4-aminophenyl)ethylcarbamate. NMR1: 1.23 (3 H, d, J = 8.8 Hz), 1.35 (9 H, s), 6.48 (2 H, d, J = 8.4 Hz).

Reference Example 5

4-(4-nitrophenyl)butanoic acid and piperidine were allowed to undergo the reaction in DMF using WSC hydrochloride and HOBt, subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to reduce the nitro group, and then reduced in the same manner as in Reference Example 2, and the resulting compound was subjected to salt formation using 4 M hydrogen chloride/ethyl acetate solution to obtain 4-(4-piperidin-1-ylbutyl)aniline dihydrochloride. F: 233.

Reference Example 6

N-methylation of N-(4-nitrophenyl)morpholine-4-carboxamide was effected by allowing it to react with sodium hydride and methyl iodide in DMF, and the resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain N-(4-aminophenyl)-N-methylmorpholine-4-carboxamide. F: 236.

Reference Examples 7 and 8

4-Fluoronitrobenzene and 2,6-dimethylmorpholine were allowed to undergo the reaction in DMF in the presence of diisopropylethylamine, and then cis and trans isomers were separated and purified by a silica gel column chromatography and respectively subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain cis-4-(2,6-dimethylmorpholin-4-yl)aniline (Reference Example 7; F: 207) and trans-4-(2,6-dimethylmorpholin-4-yl)aniline (Reference Example 8; F: 207).

Reference Example 9

2-Fluoro-4-nitrotoluene and p-formaldehyde were allowed to undergo the reaction in DMSO in the presence of sodium methoxide, and then the resulting compound was subjected to catalytic hydrogenation in the same manner as

shown in Reference Example 3 to obtain 3-fluoro-4-(2-hydroxyethyl)aniline. F: 156.

Reference Example 10

3,4,5-Trifluorobenzoic acid was allowed to react with ethanol in the presence of concentrate sulfuric acid and then allowed to react with morpholine in DMF solution, thereby obtaining 3,5-difluoro-(4-morpholin-4-yl)benzoic acid ethyl ester (EI (M^+): 271). This was further hydrolyzed in methanol with 1 M sodium hydroxide aqueous solution, and then allowed to react with DPPA in toluene in the presence of triethylamine at room temperature, heated, and further allowed to react with tert-butanol under heating, thereby obtaining a Boc compound (F: 315). By further treating with 4 M hydrogen chloride/ethyl acetate solution, 3,5-difluoro-4-(morpholin-4-yl)aniline hydrochloride was obtained. F: 215.

Reference Example 11

2-Chloro-4-{[3-(1-hydroxyethyl)phenyl]amino}pyrimidine-5-carboxylic acid ethyl ester synthesized in accordance with the method described in WO 99/31073 and 2-(3,5-dichloro-4-hydroxyphenyl)ethylamine hydrochloride were allowed to undergo the reaction at 80 to 90°C in NMP in the presence of diisopropylethylamine, and the resulting compound was

allowed to react with 1 M sodium hydroxide aqueous solution under heating in a mixed methanol-THF solution to obtain 2-{[2-(3,5-dichloro-4-hydroxyphenyl)ethyl]amino}-4-{[3-(1-hydroxyethyl)phenyl]amino}pyrimidine-5-carboxylic acid. F: 463

Reference Example 12

2,4-Dichloropyrimidine-5-carboxylic acid ethyl ester was allowed to react with sodium thiomethylate at -10°C in THF in the presence of benzyl triethylammoniumchloride and then allowed to react with tyramine hydrochloride at 70°C in NMP in the presence of diisopropylethylamine. The resulting compound was hydrolyzed in methanol using 1 M sodium hydroxide aqueous solution and then treated in NMP with aqueous ammonia in the presence of WSC hydrochloride and HOBt to convert into a carboxamide compound which was further allowed to react with m-chloroperbenzoic acid in NMP, thereby obtaining 2-{[2-(4-hydroxyphenyl)ethyl]amino}-4-(methylsulfinyl)pyrimidine-5-carboxamide. F: 321.

Reference Example 13

2-Chloro-4-(methylthio)pyrimidine-5-carboxylic acid ethyl ester was allowed to react with 4-(morpholin-4-yl)aniline at 90°C in NMP in the presence of 4 M hydrogen chloride/dioxane and further treated in the same manner as in and after the hydrolysis of Reference Example 12 to

obtain 4-(methylsulfinyl)-2-{[4-(4-oxidomorpholin-4-yl)phenyl]amino}pyrimidine-5-carboxamide. F: 378.

Reference Example 14

4-Chloro-2-methylthiopyrimidine-5-carboxylic acid ethyl ester and benzylamine were allowed to undergo the reaction in acetonitrile in the presence of diisopropylethylamine and further treated in the same manner as in and after the hydrolysis of Reference Example 12 to obtain 4-benzylamino-2-(methylsulfonyl)pyrimidine-5-carboxamide. F: 307.

Reference Example 15

2-(Benzotriazol-1-yloxy)-4-{[3-(1-hydroxyethyl)phenyl]amino}pyrimidine-5-carboxamide was synthesized in the same manner as the method of Reference Example 6 in WO 99/31073. F: 392.

Reference Example 16

2,4-Dichloropyrimidine-5-carboxylic ethyl ester and m-toluidine were allowed to undergo the reaction in acetonitrile in the presence of diisopropylamine to obtain 2-chloro-4-[(3-methylphenyl)amino]pyrimidine-5-carboxylic ethyl ester. Said ester compound was hydrolyzed in THF with 1 M sodium hydroxide aqueous solution, and the resulting carboxylic acid compound was allowed to react

with oxalyl chloride in dichloromethane in the presence of a catalytic amount of DMF and then treated with a mixture of aqueous ammonia and ice to obtain 2-chloro-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide. F: 263.

Reference Example 17

2-{[4-(Aminomethyl)phenyl]amino}-N-methyl-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide was obtained in the same manner as in Production Example 8 which is described later, using 2-chloro-N-methyl-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide and tert-butyl(4-aminophenyl)methylcarbamate. F: 363.

Reference Example 18

2-Benzyloxy-6-fluorobenzylamine was obtained by reducing 2-benzyloxy-6-fluorobenzamide in the same manner as in Reference Example 2. F: 232.

Reference Example 19

4-(2-Morpholin-4-yl-ethoxy)aniline dihydrochloride was obtained by carrying out catalytic hydrogenation of 1-[2-(4-nitrophenoxy)ethyl]morpholine in the same manner as in Reference Example 3 and then treating with 4 M hydrogen chloride/ethyl acetate. F: 223.

Reference Example 20

1-(4-Nitrophenyl)pyrroidin-3-ol and methanesulfonyl chloride were allowed to undergo the reaction in THF in the presence of triethylamine. The resulting compound and sodium cyanide were allowed to undergo the reaction in 1-methyl-2-pyrrolidone under heating. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain 1-(4-aminophenyl)pyrrolidine-3-carbonitrile. NMR2: 1.48 (9H, s), 3.12 - 3.19 (2 H, m), 6.46 - 6.50 (2 H, m).

Reference Example 21

1-(4-nitrophenyl)piperazine and N,N-dimethylglycine hydrochloride were allowed to undergo the reaction using WSC hydrochloride and HOBt in 1-methyl-2-pyrrolidone in the presence of triethylamine. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain 1-[4-(4-aminophenyl)piperazin-1-yl]-2-dimethylaminoethanone. NMR2: 2.30 (6 H, s), 3.74 - 3.76 (4 H, m), 6.64 - 6.68 (2 H, m).

Reference Example 22

2-[1-(4-Nitrophenyl)piperidin-4-yl]ethanol and methanesulfonyl chloride were allowed to undergo the reaction in THF in the presence of triethylamine. The resulting compound and morpholine were allowed to undergo

the reaction under heating in 1-methyl-2-pyrrolidine. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain 4-[4-(2-morpholin-4-ylethyl)piperidin-1-yl]aniline. NMR2 ($CDCl_3$): 3.21 - 3.45 (4 H, m), 3.71 - 3.80 (4 H, m), 6.63 - 6.66 (2 H, m).

Reference Example 23

6-(4-Nitrophenyl)morpholin-3-one was treated in the same manner as the N-methylation shown in Reference Example 6, and the resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain 6-(4-aminophenyl)-N-methylmorpholin-3-one. F: 207.

Reference Example 24

6-(4-Aminophenyl)-N-methylmorpholin-3-one was treated in the same manner as the reduction shown in Reference Example 2 and further treated with 4 M hydrogen chloride/ethyl acetate solution in ethyl acetate to obtain 4-(4-methylmorpholin-2-yl)phenylamine dihydrochloride. F: 193.

Reference Example 25

(R)-5-phenylmorpholin-3-one was allowed to react with nitric acid in concentrated sulfuric acid, and the

resulting (R)-5-(4-nitrophenyl)morpholin-3-one (F: 223) was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain (R)-5-(4-aminophenyl)morpholin-3-one. F: 193.

Reference Example 26

4-Fluoronitrobenzene and piperidin-4-one hydrochloride were allowed to undergo the reaction in THF in the presence of potassium carbonate. The resulting compound was allowed to react with sodium hydride and ethyl diethylphosphonoacetate in THF. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain [1-(4-aminophenyl)piperidin-4-yl]acetic acid ethyl ester. NMR2: 1.27 (3 H, t, J = 7.2 Hz), 2.33 (2 H, d, J = 7.2 Hz), 6.66 - 6.89 (2H, m).

Reference Example 27

(R)-5-(4-nitrophenyl)morpholin-3-one was treated with borane-THF in THF, and the resulting compound was allowed to react with di-tert-butyl dicarbonate in dichloromethane to obtain a Boc compound (F: 309) which was subsequently subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain (R)-3-(4-aminophenyl)morpholine-4-carboxylic acid tert-butyl ester. F: 279.

Reference Example 28

2-[1-(4-Nitrophenyl)piperidin-4-yl]ethanol and methane sulfonyl chloride were allowed to undergo the reaction in THF in the presence of triethylamine. The resulting compound and potassium phthalimide were allowed to undergo the reaction under heating in 1-methyl-2-pyrrolidone in the presence of potassium iodide. The resulting compound was allowed to react with hydrazine monohydrate in chloroform-methanol. The resulting compound and di-tert-butyl dicarbonate were allowed to undergo the reaction under heating in THF. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain tert-butyl {2-[1-(4-aminophenyl)-piperidin-4-yl]ethyl}-carbamate. FN: 318.

Reference Example 29

1-(4-Nitrophenyl)piperazine and N-(3-bromopropyl)phthalimide were allowed to undergo the reaction under heating in 1-methyl-2-pyrrolidone in the presence of potassium carbonate. The resulting compound was allowed to react with hydrazine monohydrate in THF. The resulting compound and di-tert-butyl dicarbonate were allowed to undergo the reaction in THF. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain tert-

butyl {3-[4-(4-aminophenyl)-piperazin-1-yl]propyl}carbamate. F: 335.

Reference Example 30

1-(4-Nitrophenyl)piperazine and ethyl 4-bromobutanoate were allowed to undergo the reaction under heating in 1-methyl-2-pyrrolidone in the presence of potassium carbonate. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain ethyl 4-[4-(4-aminophenyl)-piperazin-1-yl]butanoate. F: 264.

Reference Example 31

4-Fluoronitrobenzene and morpholine-3-carboxylic acid ethyl ester were allowed to undergo the reaction at 100°C in DMSO in the presence of diisopropylethylamine, and then the resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain 4-(4-aminophenyl)morpholine-3-carboxylic acid ethyl ester. ESI: 251.

Reference Example 32

1-(4-Nitrophenyl)piperazine and 4-bromobutyronitrile were allowed to undergo the reaction under heating in 1-methyl-2-pyrrolidone in the presence of potassium carbonate. The resulting compound was allowed to react

with polyphosphoric acid under heating and then subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain 4-[4-(4-aminophenyl)piperazin-1-yl]butanamide. F: 263.

Reference Example 33

4-Fluoronitrobenzene and 1-methylpyrrolidin-3-ol were allowed to undergo the reaction in 1-methylpyrrolidone in the presence of sodium hydride. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain 4-(1-methylpyrrolidin-3-yl)oxoaniline. F: 193.

Reference Example 34

1-(4-Nitrophenyl)piperazine and N-(3-bromopropyl)phthalimide were allowed to undergo the reaction under heating in 1-methyl-2-pyrrolidone in the presence of potassium carbonate. The resulting compound was allowed to react with hydrazine monohydrate in THF. The resulting compound was allowed to react with trimethylsilyl isocyanate in THF and then subjected to catalytic hydrogenation in the same manner as in Reference Example 3 to obtain {3-[4-(4-aminophenyl)piperazin-1-yl]propyl}urea. F: 276.

Reference Example 35

3-Fluoronitrobenzene and 2-morpholin-4-yl ethylamine were added, and the resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 and then treated with 4 M hydrogen chloride/ethyl acetate solution in ethyl acetate to obtain 3-[N-(2-morpholin-4-ylethyl)amino]aniline hydrochloride.
F: 222.

Reference Example 36

2-Morpholin-4-yl-5-nitrophenol and 4-(2-chloroethyl)morpholine were allowed to undergo the reaction in DMF in the presence of potassium carbonate, and then the resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 and further treated with 4 M hydrogen chloride/ethyl acetate solution in ethyl acetate to obtain 4-morpholin-4-yl-3-(2-morpholin-4-ylethoxy) aniline hydrochloride. F: 308.

Reference Example 37

6-Hydroxy-2-methyl-3,4-dihydro-2H-isoquinolin-1-one was allowed to react with trifluoromethanesulfonic anhydride in dichloromethane in the presence of 2,6-lutidine and dimethylaminopyridine, and the resulting compound was introduced with carbon monoxide gas in a mixture of methanol, DMF, triethylamine, palladium acetate

and 1,3-bis(diphenylphosphino)propane to obtain a methyl ester compound (F: 220). Subsequently, this was hydrolyzed in methanol with 1 M sodium hydroxide aqueous solution, allowed to react with DPPA at room temperature in toluene in the presence of triethylamine, heated, and then allowed to react with tert-butanol under heating to obtain a Boc compound (F: 277). This was further treated with 4 M hydrogen chloride/ethyl acetate solution to obtain 6-amino-2-methyl-3,4-dihydro-2H-isoquinolin-1-one hydrochloride. EI: 176.

Reference Example 38

2-Methyl-2H-isoquinolin-1-one was subjected to catalytic hydrogenation in a hydrogen atmosphere in ethanol in the presence of palladium/carbon. The resulting compound and concentrated nitric acid were allowed to undergo the reaction in concentrated sulfuric acid. The resulting compound was subjected to catalytic hydrogenation in the same manner as shown in Reference Example 3 to obtain 7-amino-2-methyl-3,4-dihydro-2H-isoquinolin-1-one. NMR2: 2.88 (2 H, t, J = 6.8 Hz), 3.13 (3 H, s), 6.95 (1 H, d, J = 8.0 Hz).

Reference Example 39

2-Methoxy-5-methylbenzamide was treated in the same manner as the reduction shown in Reference Example 2 and

further treated with 4 M hydrogen chloride/ethyl acetate solution to obtain 2-methoxy-5-methylbenzylamine. F: 152.

Reference Example 40

2-Fluoro-5-formylbenzonitrile was treated with sodium borohydride and dimethyl sulfate in THF to obtain 5-hydroxymethyl-2-fluorobenzylamine. F: 156.

Reference Example 41

2,6-Dimethoxybenzylamine was treated with 48% hydrobromic acid to obtain 2,6-dihydroxybenzylamine hydrobromide. F: 140.

Reference Example 42

By treating 3-fluorobenzonitrile with N-methylethanolamine under heating, 3-(N-2-hydroxyethyl-N-methylamino)benzonitrile was obtained (F: 177). This benzonitrile was treated in the same manner as in Reference Example 2 to obtain 3-(N-2-hydroxyethyl-N-methylamino)benzylamine. F: 181.

Reference Example 43

4-Nitrocinnamic acid and 1-methylpiperidine were condensed in the same manner as the amidation shown in Reference Example 5, and then the nitro group was reduced in ethanol using zinc powder and calcium chloride to obtain

4-[(1E)-3-(4-methylpiperazin-1-yl)-3-propen-1-ylaniline. ESI: 246.

Reference Example 44

1-Boc-piperazine and 4-nitrobenzoyl chloride were allowed to undergo the reaction in DMF in the presence of triethylamine, and then the nitro group was reduced in the sama manner as the catalytic hydrogenation shown in Reference Example 3 to obtain tert-butyl 4-(4-aminobenzoyl)piperazine-1-carboxylate. ESI: 307.

Reference Example 45

1-Boc-piperazine and 4-nitrobenzenesulfonyl chloride were allowed to undergo the reaction in DMF in the presence of triethylamine, and then the nitro group was reduced in the sama manner as the catalytic hydrogenation shown in Reference Example 3 to obtain tert-butyl 4-[(4-aminophenyl)sulfonyl]piperazine-1-carboxylate. FN: 340.

Reference Example 46

4-Iodonitrobenzene and tert-butyl 5-oxo-[1,4]diazepan-1-carboxylate were allowed to undergo the reaction in 1,2-dichlorobenzene in the presence of copper powder and potassium carbonate, and then the nitro group was reduced in ethanol using zinc powder and calcium

chloride to obtain benzyl 4-(4-aminophenyl)-5-oxo-1,4-diazepan-1-carboxylate. ESI: 340.

Reference Example 47

After allowing tert-butyl 4-[(4-nitrophenyl)acetyl]piperazine-1-carboxylate and methyl bromoacetate to undergo the reaction in DMF in the presence of sodium hydride, the nitro group was reduced in the same manner as the catalytic hydrogenation shown in Reference Example 3, and then this was treated with lithium aluminum hydride and subjected to salt formation in the same manner as in Reference Example 1 to obtain 3-(4-aminophenyl)-4-(4-methylpiperazin-1-yl)butan-1-ol trihydrochloride. ESI: 264.

Reference Example 48

1-[(4-Nitrophenyl)acetyl]piperidine was alkylated with methyl bromoacetate in the same manner as in Reference Example 47, hydrolyzed with 1 M sodium hydroxide aqueous solution in methanol, and then condensed with 1-methylpiperazine in the same manner as in Reference Example 5 to obtain 1-methyl-4-[3-(4-nitrophenyl)-4-oxo-4-piperidin-1-ylbutanoyl]piperazine (ESI: 389). This piperazine compound was subjected to the reduction of nitro group in the same manner as the catalytic hydrogenation shown in Reference Example 3 and then treated with lithium

aluminum hydride to obtain 4-[3-(4-methylpiperazin-1-yl)-1-(piperidin-1-ylmethyl)propyl]aniline. ESI: 331.

In addition, the compounds of Reference Examples 49 to 51 were obtained in the same manner as in Reference Example 2, and the compounds of Reference Examples 52 and 53 in the same manner as in Reference Example 3, the compounds of Reference Examples 54 and 55 in the same manner as the catalytic hydrogenation shown in Reference Example 3, the compounds of Reference Examples 56 to 77 in the same manner as in Reference Example 7, the compound of Reference Example 78 in the same manner as in Reference Example 9, the compounds of Reference Examples 79 to 86 in the same manner as in Reference Example 11, the compound of Reference Example 87 in the same manner as in Reference Example 12, the compound of Reference Example 88 in the same manner as in Reference Example 13, the compound of Reference Example 89 in the same manner as in Reference Example 14, the compounds of Reference Examples 90 to 103 in the same manner as in Reference Example 16, the compounds of Reference Examples 104 and 105 in the same manner as in Reference Example 19, the compounds of Reference Examples 106 and 107 in the same manner as in Reference Example 23, the compound of Reference Example 108 in the same manner as in Reference Example 25, the compound of Reference Example 109 in the same manner as in Reference Example 27, the compound of Reference Example 110 in the

same manner as in Reference Example 32, the compound of Reference Example 111 in the same manner as in Reference Example 33, the compound of Reference Example 112 in the same manner as in Reference Example 35, the compounds of Reference Examples 113 and 114 in the same manner as in Reference Example 39, the compounds of Reference Examples 115 to 118 in the same manner as in Reference Example 40, and the compound of Reference Example 119 in the same manner as in Reference Example 42. Structures and physicochemical data of the compounds of Reference Examples 49 to 119 are shown in Tables 1 to 5.

Example 1

To 8 ml NMP solution of 750 mg of 4-benzylamino-2-methylsulfonylpyrimidine-5-carboxamide were added 765 mg of 2-(3-chloro-4-hydroxyphenyl)ethylamine hydrochloride and 1.07 ml of diisopropylethylamine, followed by stirring at 110°C for 1 hour. The reaction mixture was cooled down to room temperature, and then mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, and then the solvent was evaporated. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol:aqueous ammonia) and the resulting crude crystals were recrystallized (methanol-ethyl acetate) to obtain 280 mg of 4-benzylamino-2-{[2-(3-

chloro-4-hydroxyphenyl)ethyl]amino}pyrimidine-5-carboxamide as colorless crystals.

Example 2

A 30 ml dichloromethane solution of 4.0 g of 2-chloro-4-[(3-methylphenyl)amino]pyrimidine-5-carbonyl chloride was added at -50°C to a mixture of 1.32 g of 40% methylamine aqueous solution, 2.53 ml of diisopropylethylamine and 10 ml of THF, followed by stirring for 30 minutes. This reaction mixture was poured into a mixture of 30 ml 1 M hydrochloric acid and ice and extracted with chloroform. After washing the organic layer with saturated brine and subsequently evaporating the solvent, an 800 mg portion of 3.30 g the resulting 5-carboxamide compound was made into 8 ml of NMP solution, mixed with 1.05 g of 4-(2-aminoethyl)-2,6-dichlorophenol and 1.26 ml of diisopropylethylamine, followed by stirring overnight at 80°C. The reaction mixture was cooled down to room temperature, and then mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, and then the solvent was evaporated. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol) and then recrystallized (methanol-THF) to obtain 265 mg of 2-{[2-(3,5-dichloro-4-hydroxyphenyl)ethyl]amino}-N-methyl-4-[(3-

methylphenyl)amino]pyrimidine-5-carboxamide as colorless crystals.

Example 3

A 5 ml NMP solution of 352 mg of 4-morpholinoaniline was mixed with 0.95 ml of 4 M hydrogen chloride/1,4-dioxane solution and 400 mg of 4-benzylamino-2-chloropyrimidine-5-carboxamide, followed by stirring at 90°C for 3 hours. The reaction mixture was cooled down to room temperature, and then the precipitate was collected by filtration. The collected solid was mixed with saturated sodium bicarbonate aqueous solution and extracted with a mixed solution of THF-ethyl acetate. The organic layer was washed with saturated brine, and then the solvent was evaporated. The resulting residue was crystallized by adding methanol and then recrystallized (methanol-THF) to obtain 264 mg of 4-benzylamino-2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidine-5-carboxamide as colorless crystals.

Example 4

At -7°C, 429 mg of mCPBA was gradually added to a 5 ml DMA solution of 397 mg of 4-benzylamino-2-{[4-(piperidin-1-ylmethyl)phenyl]amino}pyrimidine-5-carboxamide, followed by stirring for 30 minutes. After concentration of the reaction mixture, the resulting residue was purified by a silica gel column chromatography

(chloroform:methanol:aqueous ammonia) and then recrystallized (methanol-ethyl acetate) to obtain 228 mg of 4-benzylamino-2-({4-[(1-oxidopiperidyl-1-yl)methyl]phenyl}amino)pyrimidine-5-carboxamide as colorless crystals.

Example 5

A 10 ml 1,4-dioxane solution of 738 mg of tert-butyl 4-(4-{[5-(aminocarbonyl)-4-(benzylamino)pyrimidin-2-yl]amino}phenyl)piperidine-1-carboxylate was mixed with 2.77 ml of 4 M hydrogen chloride/1,4-dioxane solution and 3 ml of water, followed by stirring at 90°C for 2 hours. The reaction mixture was cooled down to room temperature, diluted with water, mixed with saturated sodium bicarbonate aqueous solution and then extracted with an ethyl acetate-THF mixed solution. After washing of the organic layer with saturated brine and subsequent evaporation of the solvent, the resulting solid was recrystallized (THF-ethanol) to obtain 413 mg of 4-benzylamino-2-{[4-(piperazin-1-yl)phenyl]amino}pyrimidine-5-carboxamide as ivory-colored crystals.

Example 6

A 7 ml DMF solution of 564 mg of 4-benzylamino-2-{[4-(piperidin-4-yloxo)phenyl]amino}pyrimidine-5-carboxamide was mixed with 175 mg of 35% aqueous formalin and 452 mg of

sodium triacetoxy borohydride, followed by stirring at room temperature for 2 hours. The reaction mixture was mixed with water and concentrated, and the resulting residue was purified by a silica gel column chromatography (chloroform:methanol:aqueous ammonia) and then recrystallized (THF-methanol) to obtain 273 mg of 4-benzylamino-2-{[4-(1-methylpiperidin-4-yloxo)phenyl]amino}pyrimidine-5-carboxamide as colorless crystals.

Example 7

A 20 ml portion of THF-methanol (2:1) mixed solution of 290 mg of 4-[(2-benzyloxy-6-fluorobenzyl)amino]-2-[(4-morpholin-4-ylphenyl)amino]pyrimidine-5-carboxamide synthesized in the same manner as in Production Example 13 was mixed with 50 mg of 10% palladium-carbon, followed by stirring for 1 hour in a hydrogen atmosphere. The reaction mixture was filtered and then mixed with 100 mg of 10% palladium-carbon, followed by stirring for 6 hours in a hydrogen atmosphere. After filtration of the reaction mixture and subsequent evaporation of the solvent, the resulting residue was purified by a silica gel column chromatography (chloroform-methanol). By recrystallizing the resulting crude crystals (THF-methanol), 117 mg of 4-[(2-hydroxy-6-fluorobenzyl)amino]-2-[(4-morpholin-4-

ylphenyl)amino]pyrimidine-5-carboxamide was obtained as colorless crystals.

Example 8

A 5 ml pyridine solution of 304 mg of 4-(2-aminobenzyl)amino-2-{[4-morpholin-4-yl]phenyl}amino}pyrimidine-5-carboxamide was mixed with 0.1 ml of acetic anhydride under ice-cooling and then followed by stirring at room temperature for 30 minutes. The reaction mixture was diluted with water, and then the precipitate was collected by filtration. By washing the collected solid (methanol-THF), 285 mg of 4-(2-acetylaminobenzyl)amino-2-{[4-morpholin-4-yl]phenyl}amino}pyrimidine-5-carboxamide was obtained as a colorless solid.

Example 9

A 15 ml THF-methanol (1:1) solution of 750 mg of ethyl 1-(4-{[5-(aminocarbonyl)-4-(benzylamino)pyrimidin-2-yl]amino}phenyl)piperidine-4-carboxylate was mixed with 1 M sodium hydroxide aqueous solution, followed by stirring under heating at 60°C for 1 hour. The reaction mixture was cooled down to room temperature and mixed with 1 M sodium hydroxide aqueous solution, and the precipitated solid was collected by filtration and washed with water and methanol. By recrystallizing the resulting solid from a THF-methanol

mixed solvent, 361 mg of 1-(4-{[5-(aminocarbonyl)-4-(benzylamino)pyrimidin-2-yl]amino}phenyl)piperidine-4-carboxylic acid was obtained as a colorless solid.

Example 10

Under ice-cooling, 0.05 ml of methanesulfonyl chloride was added to a mixture of 300 mg of 4-benzylamino-2-{[4-(2-aminomethylmorpholin-4-yl)phenyl]amino}pyrimidine-5-carboxamide, 0.25 ml of triethylamine and 5 ml of DMF, followed by stirring at room temperature. After concentration of the reaction mixture, the resulting residue was purified by a silica gel column chromatography (chloroform-methanol). The resulting crude crystals were dissolved in a methanol-THF mixed solution and mixed with 0.5 ml of 4 M hydrogen chloride/ethyl acetate solution, and the thus precipitated crystals were collected by filtration and further recrystallized (ethanol-water) to obtain 285 mg of 4-benzylamino-2-{[4-(2-{[(methylsulfonyl)amino]methyl}morpholin-4-yl)phenyl]amino}pyrimidine-5-carboxamide hydrochloride as a colorless solid.

Example 11

A 5 ml portion of 1-methyl-2-pyrrolidone solution of 400 mg of 4-benzylamino-2-[(4-piperazin-1-ylphenyl)amino]pyrimidine-5-carboxamide was mixed with 0.12

ml of ethyl bromoacetate and 200 mg of potassium carbonate, followed by stirring at room temperature for 30 minutes. The reaction mixture was mixed with water, and the organic layer was extracted with ethyl acetate-THF mixed solvent. The organic layer was washed with water and saturated brine and dried over anhydrous magnesium sulfate, and then the residue obtained by evaporating the solvent was washed with methanol to obtain ethyl [4-(4-{[5-(aminocarbonyl)-4-(benzylamino)pyrimidin-2-yl]amino}phenyl)piperazin-1-yl]acetate as a pale brown solid.

Example 12

A 5 ml THF-5 ml methanol solution of 680 mg of 4-benzylamino-2-{[4-(2-N-methyl-N-trifluoroacetylaminomethylmorpholin-4-yl)phenyl]amino}pyrimidine-5-carboxamide was mixed with 518 mg of potassium carbonate and 4 ml of water, followed by stirring at room temperature. The reaction mixture was mixed with ethyl acetate, washed with water and then concentrated. The resulting residue was purified by a silica gel column chromatography (chloroform-methanol-aqueous ammonia) to obtain 500 mg of crude crystals. A 120 mg portion of the crude crystals were dissolved in a methanol-THF mixed solution and mixed with 0.3 ml of 4 M hydrogen chloride/ethyl acetate solution, and the thus precipitated crystals were collected by filtration and then

recrystallized (ethanol-water) to obtain 110 mg of 4-benzylamino-2-[(4-{2-[(methylamino)methyl]morpholin-4-yl}phenyl)amino]pyrimidine-5-carboxamide dihydrochloride as a pale green solid.

Example 13

A 780 mg portion of tert-butyl (2-{1-[4-(4-benzylamino-5-carbonylpyrimidin-2-ylamino)phenyl]piperidin-4-yl}ethyl)carbamate was mixed with 10 ml of trifluoroacetic acid, followed by stirring at room temperature for 1 hour. The solvent was evaporated, the resulting residue was mixed with 1 M sodium hydroxide, and the thus formed solid was collected by filtration. The solid was dissolved in chloroform-methanol, washed with saturated brine and then dried with anhydrous magnesium sulfate. The solvent was evaporated, and the resulting residue was dissolved in chloroform-methanol and mixed with 4 M hydrogen chloride/dioxane solution. The solvent was evaporated, and the resulting residue was recrystallized from THF-methanol-water to obtain 215 mg of 2-({4-[4-(2-aminoethyl)piperidin-1-yl]phenyl}amino)-4-(benzylamino)pyrimidine-5-carboxamide trihydrochloride as a colorless solid.

Example 14

A 5 ml methanol solution containing 80 mg of 4-(benzylamino)-2-{[4-(β-D-acetylglucopyranosyloxy)phenyl]amino}pyrimidine-5-carboxamide was mixed with sodium methoxide, followed by stirring overnight at room temperature. The reaction mixture was filtered by adding an ion exchange resin (Dowex 50WX8-100) and then concentrated, and the resulting crystals were washed with methanol to obtain 22 mg of 4-(benzylamino)-2-{[4-(β-D-glucopyranosyloxy)phenyl]amino}pyrimidine-5-carboxamide as pale brown crystals.

Example 15

A 10 ml portion of 1-methyl-2-pyrrolidone solution containing 800 mg of 2-{[4-(piperidin-4-yloxy)phenyl]amino}-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide was mixed with 0.12 ml of methyl iodide and 300 mg of potassium carbonate, followed by stirring at room temperature for 1 hour and then at 60°C for 30 minutes. A 0.1 ml portion of methyl iodide was further added thereto, followed by stirring for 30 minutes. The reaction mixture was cooled down to room temperature, mixed with water and then extracted with an ethyl acetate-THF mixed solvent. The organic layer was washed with water and saturated brine and

then dried over anhydrous magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by a silica gel column chromatography (chloroform-methanol-aqueous ammonia) and further recrystallized from ethanol to obtain 197 mg of 2-({4-[(1-methylpiperidin-4-yl)oxy]phenyl}amino)-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide as colorless crystals.

Production Example 1

A 6 ml portion of NMP solution containing 600 mg of 2-(benzotriazol-1-yloxy)-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide was mixed with 538 mg of 2-(3-bromo-4-hydroxyphenyl)ethylamine and 0.72 ml of diisopropylethylamine, followed by stirring at 80°C for 2 hours. The reaction mixture was cooled down to room temperature, and then mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, the solvent was evaporated, and then the resulting residue was recrystallized (ethanol-THF) to obtain 200 mg of 2-{[2-(3-bromo-4-hydroxyphenyl)ethyl]amino}-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide as colorless crystals.

Production Example 2

A 6 ml portion of NMP solution containing 533 mg of 2-chloro-4-[(3-ethylphenyl)amino]pyrimidine-5-carboxamide was mixed with 624 mg of 2-(3-chloro-4-hydroxyphenyl)ethylamine hydrochloride and 0.87 ml of diisopropylethylamine, followed by stirring at 80°C for 4 hours. The reaction mixture was cooled down to room temperature, and then mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, the solvent was evaporated, and then the resulting residue was recrystallized (methanol-THF) to obtain 460 mg of 2-{[2-(3-chloro-4-hydroxyphenyl)ethyl]amino}-4-[(3-ethylphenyl)amino]pyrimidine-5-carboxamide as colorless crystals.

Production Example 3

A 8 ml portion of NMP solution containing 800 mg of 2-{[2-(4-hydroxyphenyl)ethyl]amino}-4-(methylsulfinyl)pyrimidine-5-carboxamide was mixed with 373 mg of cyclohexylamine and 0.87 ml of diisopropylethylamine, followed by stirring at 100°C for 1 hour. The reaction mixture was cooled down to room temperature, and then mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, and then the solvent was evaporated. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol), and

the resulting crude crystals were recrystallized (methanol-ethyl acetate) to obtain 547 mg of 2-{[2-(4-hydroxyphenyl)ethyl]amino}-4-cyclohexylaminopyrimidine-5-carboxamide as colorless crystals.

Production Example 4.

A 4 ml portion of DMF solution containing 352 mg of 2-{[2-(4-hydroxyphenyl)ethyl]amino}-4-[(3-methylphenyl)amino]pyrimidine-5-carboxylic acid was mixed with 223 mg of WSC hydrochloride, 157 mg of HOBt and 103 mg of 2-dimethylaminoethylamine, followed by stirring overnight at room temperature. The reaction mixture was diluted with water and then extracted with ethyl acetate. The organic layer was washed with saturated brine and then the solvent was evaporated. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol:aqueous ammonia) and then recrystallized (hexane-ethyl acetate) to obtain 291 mg of N-(2-dimethylaminoethyl)-2-{[2-(4-hydroxyphenyl)ethyl]amino}-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide as colorless crystals.

Production Example 5

A 10 ml portion of NMP solution containing 500 mg of 2-{[4-(aminomethyl)phenyl]amino}-4-[(3-

methylphenyl)amino]pyrimidine-5-carboxamide dihydrochloride synthesized by the method described in Example 8 of WO 99/31073 was mixed with 0.53 ml of triethylamine and 0.12 ml of acetic anhydride, followed by stirring overnight at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate, the organic layer was washed with saturated brine and then the solvent was evaporated. The resulting residue was triturated with methanol, and washed to obtain 270 mg of 2-({4-[(acetylamino)methyl]phenyl}amino)-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide as a pale yellow solid.

Production Example 6

A 20 ml acetic acid-10 ml THF mixed solution containing 500 mg of 2-{[4-(aminomethyl)phenyl]amino}-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide dihydrochloride was mixed with 5.76 g of potassium cyanate, which was added by dividing into 6 portions, at room temperature, followed by stirring for 6 hours. The reaction mixture was concentrated and then poured into water, and the precipitated solid was collected by filtration and washed with acetonitrile. The resulting solid was purified by a silica gel column chromatography (chloroform:methanol) to obtain 150 mg of 4-[(3-methylphenyl)amino]-2-[(4-

ureidomethylphenyl)amino]pyrimidine-5-carboxamide as a pale yellow solid.

Production Example 7

A 10 ml portion of NMP solution containing 1.0 g of 2-{[4-(aminomethyl)phenyl]amino}-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide dihydrochloride was mixed with 0.83 ml of triethylamine and, under ice-cooling, with 0.4 ml of trifluoroacetic anhydride, followed by stirring at room temperature for 2 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. After washing the organic layer with saturated brine, the solvent was evaporated, and the residue was crystallized from chloroform-hexane to obtain 660 mg of a trifluoroacetylamino compound. A 7 ml portion of DMF solution containing 640 mg of the trifluoroacetylamino compound was mixed with 400 mg of potassium carbonate and 0.11 ml of iodomethane, followed by stirring overnight at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate, the organic layer was washed with saturated brine, and then the solvent was evaporated. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol) to obtain 280 mg of an N-methyl compound. A 5 ml methanol-5 ml THF mixed solution containing 160 mg of the N-methyl compound was mixed with 2 ml of concentrated aqueous ammonia,

followed by stirring overnight at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate, the organic layer was washed with saturated brine, and then the solvent was evaporated. The resulting solid was recrystallized (methanol-water) to obtain 100 mg of 2-({4-[(methylamino)methyl]phenyl}amino)-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide as colorless crystals.

Production Example 8

A mixture of 1.0 g of 2-chloro-4-(3-methylanilino)pyrimidine-5-carboxamide, 1.6 g of tert-butyl 4-aminobenzyl(2-morpholin-4-ylethyl)carbamate, 1.33 ml of diisopropylethylamine and 10 ml of NMP was stirred overnight at 130°C. The reaction mixture was cooled down to room temperature, and then mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, the solvent was evaporated, and the resulting residue was purified by a silica gel column chromatography (chloroform:methanol). Then, a 750 mg portion of 780 mg of the resulting compound was stirred overnight at room temperature in a mixed solution of 75 ml methanol and 30 ml 6 M hydrochloric acid. The reaction mixture was concentrated, and then the resulting crystals were washed with methanol to obtain 510 mg of 4-[(3-methylphenyl)amino]-2-[(4-{[(2-morpholin-4-

ylethyl)amino]methyl}phenyl)amino]pyrimidine-5-carboxamide trihydrochloride as colorless crystals.

Production Example 9

A 7 ml portion of DMF solution containing 685 mg of 2-{[4-(aminomethyl)phenyl]amino}-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide dihydrochloride was mixed with 0.45 ml of triethylamine, 420 mg of 35% aqueous formalin and 1.09 g of sodium triacetoxy borohydride, followed by stirring overnight at room temperature. The reaction mixture was mixed with water, concentrated and then purified by a silica gel column chromatography (chloroform:methanol:aqueous ammonia) to obtain crude crystals. This was dissolved in a methanol-ethyl acetate mixed solution and mixed with 1 ml of 4 M hydrogen chloride/ethyl acetate solution, and the thus precipitated crystals were collected by filtration and further recrystallized (methanol-water) to obtain 164 mg of 2-({4-[(dimethylamino)methyl]phenyl}amino)-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide dihydrochloride as colorless crystals.

Production Example 10

A mixture of 2.0 g of 2-chloro-4-{(3-methylphenyl)amino}pyrimidine-5-carboxamide, 1.25 g of 4-aminophenetyl alcohol, 1.99 ml of diisopropylethylamine and

10 ml of NMP was stirred overnight at 110°C. The reaction mixture was cooled down to room temperature and mixed with water and ethyl acetate, and the thus precipitated solid was collected by filtration and recrystallized (methanol) to obtain 560 mg of 2-{[4-(2-hydroxyethyl)phenyl]amino}-4-[(3-methylphenyl)amino]pyrimidine-5-carboxamide as pale yellow crystals.

Production Example 11

A 5 ml portion of NMP solution containing 300 mg of 4-benzylamino-2-(methylsulfonyl)pyrimidine-5-carboxamide was mixed with 122 mg of p-anisidine and 58 mg of potassium fluoride, followed by stirring at 90 to 100°C for 21 hours. During this period, 58 mg of potassium fluoride was added three times. The reaction mixture was cooled down to room temperature, diluted with water, mixed with saturated sodium bicarbonate aqueous solution and then extracted with ethyl acetate. The organic layer was washed with saturated brine, and then the solvent was evaporated. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol) and then recrystallized (methanol-THF) to obtain 82 mg of 4-benzylamino-2-[(4-methoxyphenyl)amino]pyrimidine-5-carboxamide as colorless crystals.

Production Example 12

A 6 ml portion of NMP solution containing 303 mg of 4-cyclohexylamino-2-(methylsulfonyl)pyrimidine-5-carboxamide was mixed with 1.05 ml of 1 M n-tetrabutylammonium fluoride/THF solution, followed by stirring at 90°C for 1 hour. Next, this was mixed with 200 mg of 4-morpholinoaniline and 2.77 ml of 4 M hydrogen chloride/1,4-dioxane solution, followed by stirring at 90°C for 3 hours. The reaction mixture was cooled down to room temperature, diluted with water, mixed with saturated sodium bicarbonate aqueous solution and then extracted with ethyl acetate-THF mixed solution. The organic layer was washed with saturated brine, and then the solvent was evaporated and the resulting residue was purified by a silica gel column chromatography (chloroform:methanol) to obtain 54 mg of 4-cyclohexylamino-2-[(4-morpholinophenyl)amino]pyrimidine-5-carboxamide as a pale brown solid.

Production Example 13

A mixture of 450 mg of 4-methylsulfinyl-2-({4-[(N-oxidomorpholin-4-yl)methyl]phenyl}amino)pyrimidine-5-carboxamide, 0.29 ml of isopropylamine, 0.24 ml of diisopropylethylamine and 5 ml of DMA was stirred at 80°C for 3 hours. The reaction mixture was cooled down to room temperature, mixed with 8 ml of 5% sodium hydrogen sulfite,

followed by stirring for 1 hour. The reaction mixture was adjusted to pH 9 by adding 0.5 ml of concentrated aqueous ammonia, diluted with water and then extracted with chloroform. The organic layer was washed with saturated brine, and then the solvent was evaporated. The resulting residue was purified by a silica gel column chromatography (chloroform:methanol:aqueous ammonia), and the resulting pale brown oil was crystallized from ethyl acetate to obtain 50 mg of 2-{[4-(morpholinomethyl)phenyl]amino}-4-(2-propylamino)pyrimidine-5-carboxamide as colorless crystals.

Production Example 14

A 1 ml portion of chloroform solution containing 11.7 mg of 4-methylsulfinyl-2-({4-[(N-oxidomorpholin-4-yl)methyl]phenyl}amino)pyrimidine-5-carboxamide was mixed with 5.1 mg of cyclopropylamine and 5.8 mg of diisopropylethylamine, followed by stirring at 90°C for 15 hours. A 1 ml portion of aqueous solution containing 50 mg of sodium hydrogen sulfite was added to the reaction mixture, followed by stirring at room temperature for 4 hours. This was mixed with 0.1 ml of aqueous ammonia and extracted with 2 ml of chloroform. By evaporating the solvent under a reduced pressure and fractionating the residue by an HPLC (Wakosil-II 5C18AR, 0.1% $HCOOH-H_2O/MeOH$ = 7/3 - 0/10), 2.6 mg of 4-cyclopropylamino-2-(4-morpholin-

4-ylmethylphenylamino)-pyrimidine-5-carboxamide was obtained.

Production Example 15

A 1 ml portion of THF solution containing 7.9 mg of 4-benzylamino-2-chloropyrimidine-5-carboxamide and 3.7 mg of aniline, followed by stirring at 90°C for 20 hours, which was then mixed with 60 mg of PS-tosyl chloride (mfd. by Argonaut Technologies, 2.44 mmol/g), followed by stirring at room temperature for 3 hours. The reaction mixture was mixed with 2 ml of saturated sodium bicarbonate aqueous solution and extracted with 2 ml of chloroform. By evaporating the solvent under a reduced pressure, 6.6 mg of 4-benzylamino-2-phenylaminopyrimidine-5-carboxamide was obtained.

Production Examples 16 to 57

A 960 mg portion of 2-{[2-(4-hydroxyphenyl)ethyl]amino}-4-(methylsulfinyl)pyrimidine-5-carboxamide was dissolved in 100 ml of n-butanol and dispensed in 1.0 ml portions into 96 test tubes. DMF 1.0 M solutions of corresponding amine compounds were added in 50 μl portions, followed by stirring at 100°C for 10 hours. The solvent was evaporated under a reduced pressure, and each of the resulting crude products was dissolved in 500 μl of methanol and purified by HPLC fractionation using the

molecular weight as the trigger by simultaneous measurement of MS, thereby obtaining the compounds of Production Examples 16 to 57.

Production Examples 58 to 73

Each of 2-chloro-4-(substituted amino)pyrimidine-5-carboxylic acids having various substituting amino groups on the 4-position of pyrimidine was mixed with Rink Amide AM resin, which is prepared as an amine form by removal of Fmoc protecting group by piperazine treatment, and with a mixed solvent of dichloromethane and DMF, further mixed with diisopropyl carbodiimide, followed by stirring at room temperature for 5 hours. The resin was collected by filtration and washed with dichloromethane, DMF, THF and methanol in that order. The same series of washing was repeated once again, and finally washed with diethyl ether. By drying the resin under a reduced pressure, various types of 2-chloro-4-(substituted amino)pyrimidine-5-carboxamide (resin) adhered to the resin via the nitrogen atom of amido moiety were obtained. The resulting resins were respectively added in 100 mg (equivalent to 40 μM) portions to two wells of the reaction vessel of a synthesizer (SY-2000, Shimadzu Corp.). A 1.0 ml portion of 0.5 M NMP solution of tyramine hydrochloride or 2-(3-chloro-4-hydroxyphenyl)ethylamine hydrochloride and 200 μl of 2.5 M NMP solution of diisopropylethylamine were added to each

well and shaken at 100°C for 12 hours. After discarding the reaction mixture by filtration, each resin was washed with DMF (twice), dichloromethane, DMF, THF, methanol and THF in that order. The resin was mixed with 4 ml of dichloromethane solution of 40% trifluoroacetic acid and shaken at room temperature for 5 minutes. Each resin was removed by filtration to collect the reaction mixture. By evaporating the solvent under a reduced pressure, each of the compounds of Production Examples 58 to 73 was obtained. Samples of compounds having a purity of 50% or less were purified by HPLC fractionation using the molecular weight as the trigger by simultaneous measurement of MS.

Production Examples 74 to 93

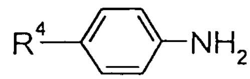
A 1.09 g portion of 2-[2-(4-hydroxyphenyl)ethylamino]-4-[(3-methylphenyl)amino]pyrimidine-5-carboxylic acid was dissolved in 200 ml of DMF and dispensed in 2.0 ml portions into 96 test tubes. A 35 μl portion of 1.0 M HOBt/DMF solution and 70 mg of a PS-carbodiimide resin (mfd. by Argonaut Technologies) (1.0 - 1.5 mmol/g) were added to each test tube. Subsequently, 1.0 M DMF solutions of amine compounds corresponding to the target compounds were added in 25 μl portions and shaken overnight at room temperature. By adding 70 mg of PS-tris amine resin (3 - 5 mmol/g) and stirring at room temperature for 3 hours, unreacted 2-{2-

[(4-hydroxyphenyl)ethyl]amino}-4-[(3-methylphenyl)amino]pyrimidine-5-carboxylic acid and HOBt were bonded to the PS-tris amine resin. By removing the resin by filtration and evaporating the solvent under a reduced pressure, the compounds of Production Examples 74 to 93 were obtained.

The compounds of Examples 16 to 258 and Production Examples 94 to 275 shown in the following Tables 6 to 20 were respectively obtained in the same manner as the methods of the aforementioned Examples or Production Examples. Structures and physicochemical data of the compounds of Examples 1 to 258 and Production Examples 1 to 275 are shown in the following Tables 6 to 20.

In addition, structures of other compounds of the present invention are shown in Tables 21 to 25. These may be easily synthesized by using the methods described in the aforementioned production methods and examples and the methods obvious to those skilled in the art, or modified methods thereof.

Table 1



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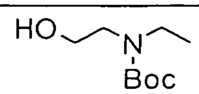
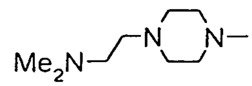
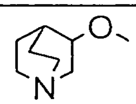
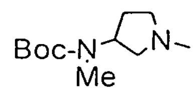
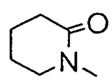
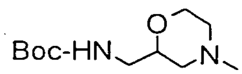
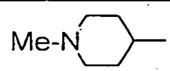
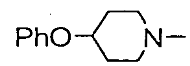
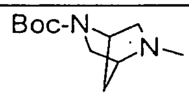
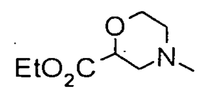
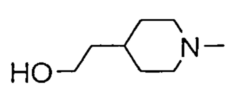
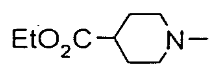
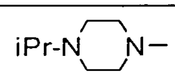
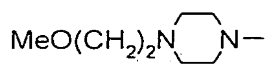
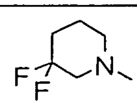
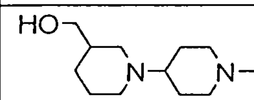
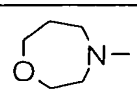
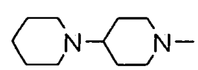
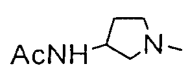
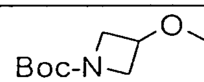
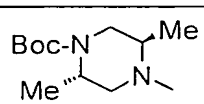
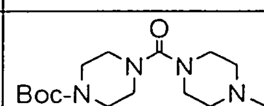
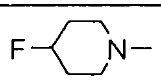
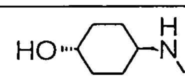
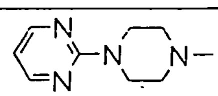
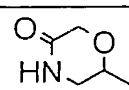
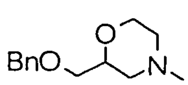
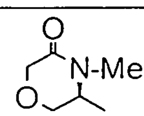
52		F: 267	66		NMR2:2.27(6H,s), 3.05-3.08 (4H, m), 3.63-6.67(2H,m)
53		F: 219	67		NMR2:1.48(9H,s), 3.12-3.19 (2H, m), 6.46-6.50 (2H,m)
54		F: 191	68		F:338
55		F: 191	69		F: 269 Sal: HCl
56		F: 290	70		F: 250
57		NMR2: 2.55-2.61(2H, m), 3.72-3.75(2H,m) 6.62-6.66(2H,m)	71		NMR2: 1.26 (3H, t, J=7.2Hz),3.40-3.48 (4H,m),6.62-6.66(2H, m)
58		F: 220	72		F: 236
59		F: 213 Sal: HCl	73		ESI: 290
60		F: 193 Sal: 2HCl	74		ESI: 260
61		F:220	75		EI: 265
62		F: 306	76		ESI: 390
63		F: 195 Sal: HCl	77		ESI: 207
64		F: 256 Sal:HCl	104		EI:193 Sal:HCl
65		ESI:299	106		F: 207

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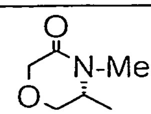
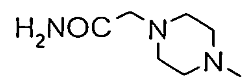
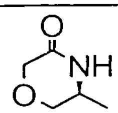
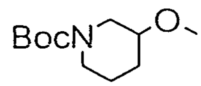
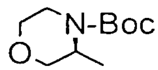
107		F: 207	110		NMR1:2.89(2H, s),2.92-2.95(4H,m) 6.47-6.50 (2H,m)
108		F: 193	111		NMR2:1.46(9H, s), 4.05-4.08 (1H, m), 6.67-6.79(2H, m)
109		F: 279			

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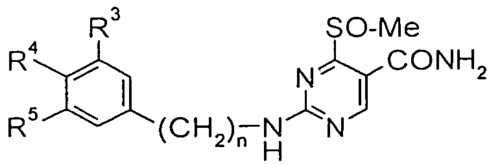

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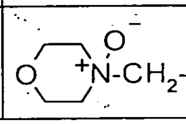
88	H		H	0	F: 392

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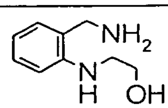
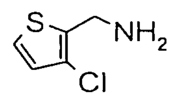
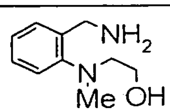
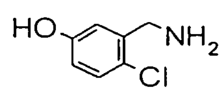
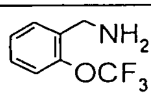
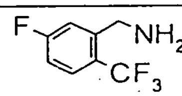
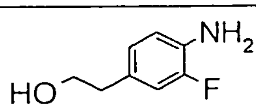
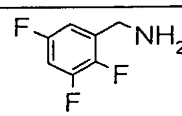
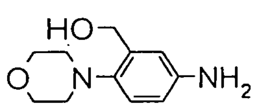
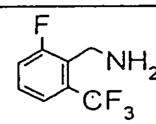
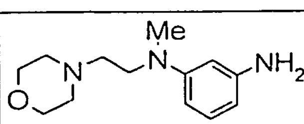
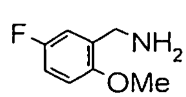
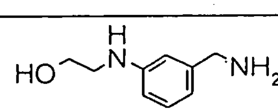
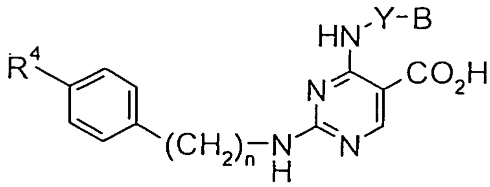
49		F:167	113		F:148 Sal HCl
50		F:181	114		F:158
51		F:192 Sal HCl	115		F:194 Sal HCl
78		F: 156	116		F:162 Sal HCl
105		F: 209 Sal HCl	117		F:194 Sal HCl
112		EI: 236 Sal HCl	118		F:156 Sal HCl
			119		F:167

Table 4



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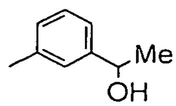
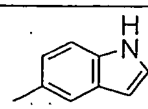
80	$HOCH_2CH_2$	0		F: 395
81	$HOCH_2CH_2$	0		FN: 388
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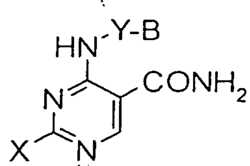
84	$HOCH_2CH_2$	0	2,5-F_2-Ph	F: 387
85	$HOCH_2CH_2$	0	3,4-F_2-Ph	NMR: 2.69(2H, t, J=7.1Hz), 7.32-7.44(2H, m), 8.70(1H, s)
86	$HOCH_2CH_2$	0	2,4-F_2-Ph	NMR: 2.67(2H, t, J=7.1Hz), 7.07-7.09(4H, m), 8.69(1H, s)

Table 5



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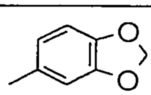
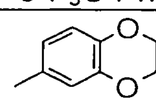
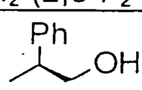
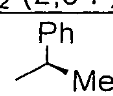
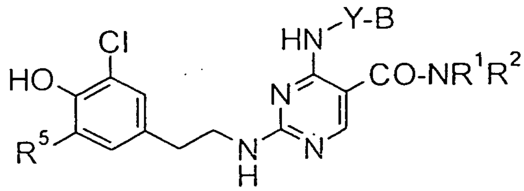
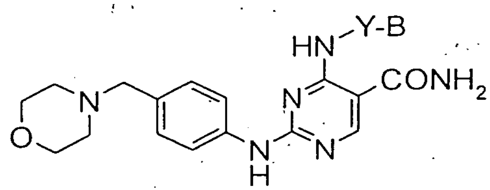
89	cHex	$MeSO_2$	F: 299	97	3-Et-Ph	Cl	F: 277
90	3-CN-Ph	Cl	F: 274	98	3-F_3C-Ph	Cl	F: 317
91		Cl	F: 293	99		Cl	FN: 305
92	Bn	Cl	F: 263	100	-CH_2-(2-F-Ph)	Cl	F: 281
93	-CH_2-(2,6-F_2-Ph)	Cl	F: 299	101	-CH_2-(2,5-F_2-Ph)	Cl	F: 299
94		Cl	F: 293	102		Cl	F: 277
95	-CH_2-(2-F_3C-Ph)	Cl	FN: 329	103	-CH_2-(2-O_2N-Ph)	Cl	F: 308
96	-CH_2-(2,3,6-F_3-Ph)	Cl	F: 317				

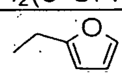
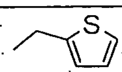
Table 6



Ex	Syn	R^5	R^1	R^2	-Y-B	Dat
1	Ex 1	H	H	H	Bn	F: 398 ; NMR1: 4.60-4.66(2H, br m), 8.38(0.7H, s),8.45(0.3H, s),9.87(1H, s)
2	Ex 2	Cl	Me	H	3-Me-Ph	F: 446 ; NMR1: 2.75-2.79 (5H, m), 8.49(0.7H, s), 8.54(0.3H,s), 9.88(1H,s)
16	Ex 1	Cl	H	H	Bn	F: 432 ; NMR1: 4.60-4.66(2H, br m), 8.38(0.7H, s),8.45(0.3H, s),9.85(1H, s)
17	Pre 3	Cl	H	H	CH_2-(2,5-F_2-Ph)	F: 468

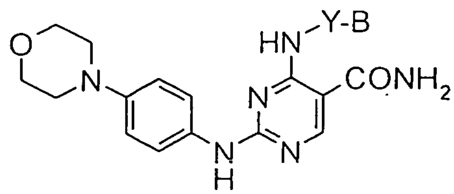
Table 7

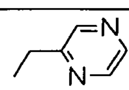


Ex	Syn	-Y-B	Dat
18	Ex 3	Bn	F: 419
19	Pre 14	CH_2(3-Cl-Ph)	F: 453
20	Pre 14		F: 409
21	Pre 14		F: 425
22	Pre 14	CH_2-2Py	F: 420
23	Pre 14	CH_2-3Py	F: 420
24	Pre 14	CH_2-4Py	F: 420

Ex	Syn	-Y-B	Dat
25	Pre 14	CH_2(2-Cl-Ph)	F: 453
26	Pre 14	CH_2(2-F_3C-Ph)	F: 487
27	Pre 14	CH_2(2-MeO-Ph)	F: 449
28	Pre 14	CH_2(3-F_3C-Ph)	F: 487
29	Pre 14	CH_2(3-MeO-Ph)	F: 449
30	Pre 14	CH_2(4-Cl-Ph)	F: 453
31	Pre 14	CH_2(4-F_3C-Ph)	F: 487
32	Pre 14	CH_2(4-MeO-Ph)	F: 449

Table 8



Ex	Syn	-Y-B	Dat
3	Ex 3	Bn	F: 405 ; NMR1: 3.71-3.74(4H, m), 4.66(2H, d, J=6.3Hz), 7.33-7.35 (4H, m), 8.51(1H, s)
7	Ex 7	CH_2-(2-F-6-HO-Ph)	F: 439 ; NMR1: 3.70-3.73(4H, m), 7.13-7.19 (1H, m),8.47(1H, s), 10.25(1H, s)
8	Ex 8	CH_2-(2-AcHN-Ph)	F:462
33	Pre 13	CH_2-(2-Me-Ph)	F: 419
34	Pre 13	CH_2-(2-Cl-Ph)	F: 439 ; NMR1: 2.95-3.03(m, 4H), 4.72(d, 2H, J=5.9Hz), 7.48-7.53(m, 1H), 8.53(s, 1H)
35	Pre 13	CH_2-(2-MeO-Ph)	F: 435 ; NMR1: 2.97-3.05(m, 4H), 3.85(s, 3H), 4.61(d, 2H, J=5.8Hz), 8.50(s, 1H)
36	Pre 13	CH_2-(2,4-F_2-Ph)	F: 441
37	Pre 13	CH_2-(2,3,6-F_3-Ph)	F: 459 ; NMR1: 3.00-3.08(m, 4H), 4.83(d, 2H, J=5.9Hz), 7.43-7.52 (1H, m),8.52(s, 1H)
38	Pre 13	CH_2-(3,5-F_2-Ph)	F: 441 ; NMR1: 2.98-3.03(m, 4H), 4.66(d, 2H, J=5.8Hz), 7.04-7.12(m, 1H), 8.52(s, 1H)
39	Pre 13	CH_2-(2-F-5-Cl-Ph)	FN: 455 ; NMR1: 2.98-3.04(4H, m), 4.67(d, 2H, J=5.8 Hz), 7.34-7.39(m, 1H), 8.53(1H, s)
40	Pre 13	CH_2-(2-HO-Ph)	F: 421
41	Pre 13	CH_2-(3-MeO-Ph)	F: 435 ; NMR1: 2.97-3.05(4H, m), 3.70(s, 3H), 4.62(2H, d, J=5.4Hz), 8.51(1H, s)
42	Pre 13	CH_2-(2,5-$(MeO)_2$-Ph)	F: 465 ; NMR1: 2.96-3.04(4H, m), 3.80(s, 3H), 4.58(2H, d, J=4.7Hz), 8.50(1H, s)
43	Pre 13	CH_2-(3-F-Ph)	F: 423 ; NMR1: 2.97-3.04(4H, m), 4.67(2H, d, J=5.9Hz), 7.34-7.41(m, 1H), 8.52(1H, s)
44	Pre 13	CH_2-(3-F_3C-Ph)	F: 473 ; NMR1: 2.96-3.03(4H, m), 4.75(2H, d, J=5.8Hz), 6.95-7.04(m, 2H), 8.52(1H, s)
45	Pre 13	CH_2-(2,3-$(MeO)_2$-Ph)	F: 465 ; NMR1: 2.97-3.03(4H, m), 3.82(s, 3H), 4.64(2H, d, J=5.9Hz), 8.50(1H, s)
46	Pre 13		F: 407
47	Pre 13	CH_2-(3-$HOCH_2$-Ph)	F: 433 ; NMR1: 2.95-3.04(4H, m), 4.60(2H, d, J=5.3Hz), 4.68(2H, d, J=5.9Hz), 8.51(1H, s)
48	Pre 13	CH_2-(2,3-F_2-Ph)	F: 441 ; NMR1: 2.97-3.03(4H, m), 4.74(2H, d, J=5.9Hz), 7.28-7.36(m, 1H), 8.53(1H, s)
49	Pre 13	CH_2-(4-F-Ph)	F: 423
50	Pre 13	CH_2-(2-EtO-Ph)	F: 449
51	Pre 13	CH_2-(2,4-$(MeO)_2$-Ph)	F: 465
52	Pre 13	CH_2-(2,6-Me_2-Ph)	F: 433

(Table 8 continued)

53	Pre 13	CH_2-(2-F-5-Me-Ph)	F: 437 ; NMR1: 2.20(3H, s), 4.66(2H, d, J=4.5Hz), 7.08-7.11 (3H, m),8.51(1H, s)
54	Pre 13	CH_2-(2-(Et_2NCH_2)-Ph)	F: 490
55	Pre 13	CH_2-(3-HO-Ph)	F: 421 ; NMR1: 2.96-3.05(4H, m), 4.58(2H, d, J=5.9Hz), 8.51(1H, s)
56	Pre 13	CH_2-(3,5-$(MeO)_2$-Ph)	F: 465
57	Pre 13	CH_2-(2-Me-3-Cl-Ph)	FN: 451
58	Pre 13	CH_2-(2-Cl-6-F-Ph)	F: 457 ; NMR1: 3.00-3.06(4H, m), 4.84(2H, d, J=4.4Hz), 8.52(1H, s)
59	Pre 13	CH_2-(2,6-F_2-3-Cl-Ph)	FN: 473 ; NMR1: 3.01-3.07(4H, m), 4.82(2H, d, J=5.4Hz), 7.18-7.26(m, 1H), 8.52(1H, s)
60	Pre 13	CH_2-(2-F-6-MeO-Ph)	F: 453 ; NMR1: 3.01-3.06(4H, m), 3.86(3H, s), 4.70(2H, d, J=4.9Hz), 8.48(1H, s)
61	Pre 13	CH_2-(2,6-Cl_2-Ph)	F: 473 ; NMR1: 3.01-3.06(4H, m), 4.92(2H, d, J=4.9Hz), 7.39-7.45(m, 1H), 8.53(1H, s)
62	Ex 3	CH_2-(2-F-Ph)	F: 423 ; NMR1: 3.01-3.03(4H, m), 4.71(2H, d, J=5.9Hz), 7.12-7.16 (1H, m),8.52(1H, s)
63	Ex 3	CH_2-(2,6-F_2-Ph)	F: 441 ; NMR1: 4.79(2H, d, J=5.8Hz), 7.40-7.47(1H, m), 8.52(1H, s)
64	Ex 3	CH_2-(2,5-F_2-Ph)	F: 441 ; NMR1: 2.97-3.05(4H, m), 4.68(2H, d, J=5.9Hz), 7.28-7.33 (1H, m),8.53(1H, s)
65	Ex 3	CH_2-(2-F_3C-Ph)	F: 473
66	Pre 13	CH_2-(2-$HOCH_2$-Ph)	F: 434 ; NMR1: 3.69-3.75(4H, m), 4.47(2H, d, J=5.3Hz), 4.65(2H, d, J=5.8Hz), 8.51(1H, s)
67	Pre 13	CH_2-(2-OMe-6-Me-Ph)	F: 449 ; NMR1: 3.70-3.75(4H, m), 3.81(3H, s), 4.65(2H, d, J=5.3Hz), 8.47(1H, s)
68	Pre 13	CH_2-[2-$HO(CH_2)_2O$-Ph]	F: 465 ; NMR1: 3.69-3.75(4H, m), 4.05(2H, t, J=4.9Hz), 4.65(2H, d, J=5.9Hz), 8.49(1H, s)
69	Pre 13	CH_2-(2-OH-5-Cl-Ph)	F: 455 ; NMR1: 3.71-3.76(4H, m), 4.56(2H, d, J=5.9Hz), 7.07-7.13(m, 1H), 8.50(1H, s)
70	Pre 13	CH_2-(2-F-5-$HOCH_2$-Ph)	F:453 ; NMR1: 3.71-3.74(4H, m), 4.40(2H, d, J=5.9Hz), 4.70(2H, d, J=5.9Hz), 8.52(1H, s)
71	Pre 13	CH_2-[2-$HO(CH_2)_2HN$-Ph]	F: 464 Sal: 3HCl
72	Pre 13	CH_2[2-$HO(CH_2)_2N(Me)$-Ph]	F:478 ; NMR1: 2.70 (3H, s) 3.52-3.57(2H, m) 3.70-3.73(4H, m), 4.74(2H, d, J=5.8Hz), 8.52 (1H, s)
73	Pre 13	CH_2-(3-Et_2NCH_2-Ph)	F:490
74	Pre 13	CH_2-[2,6-$(MeO)_2O$-Ph]	F: 465 ; NMR1: 3.71-3.75(4H, m), 3.79(6H, s), 4.66(2H, d, J=4.9Hz), 8.46(1H, s)
75	Pre 13	CH_2-[3-$HO(CH_2)_2O$-Ph]	F: 465 ; NMR1: 3.70-3.75(4H, m), 3.91(2H, t, J=4.9Hz), 4.63(2H, d, J=6.4Hz), 8.51(1H, s)
76	Pre 13	CH_2-(2-CF_3O-Ph)	F: 489
77	Pre 13	CH_2-(2-F-6-CF_3-Ph)	F: 491 ; NMR1: 3.70-3.75(4H, m), 4.85(2H, d, J=4.0Hz), 7.62-7.71(m, 5H), 8.53(1H, s)
78	Pre 13	CH_2-(3-F-6-CF_3-Ph)	F: 491 ; NMR1: 3.69-3.74(4H, m), 4.86(2H, d, J=5.9Hz), 7.85-7.91(m, 1H), 8.56(1H, s)

(Table 8 continued)

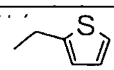
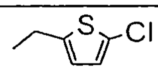
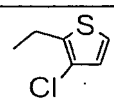
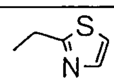
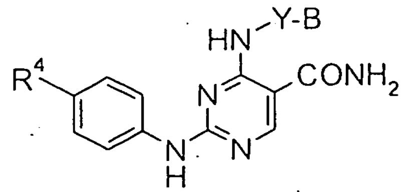
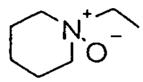
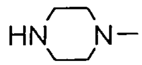
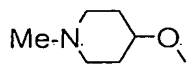
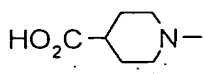
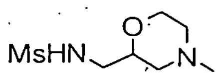
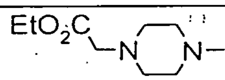
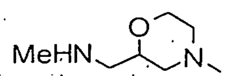
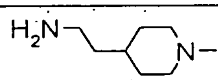
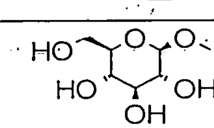
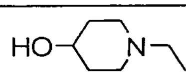
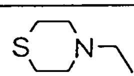
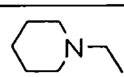
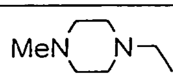
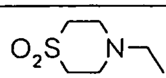
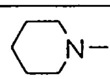
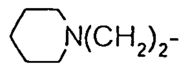
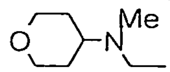
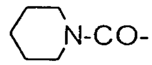
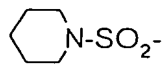
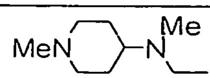
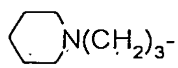
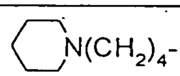
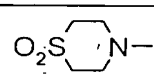
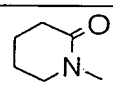
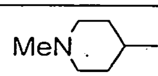
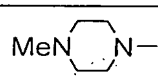
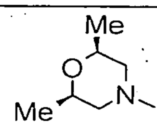
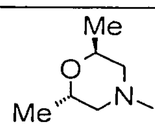
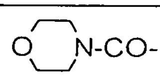
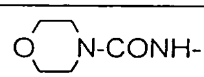
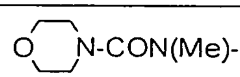
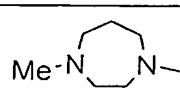
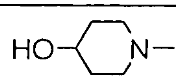
79	Pre 13	CH_2-(2-F-3-CF_3-Ph)	F: 491
80	Pre 13	CH_2-[2-HO$(CH_2)_3$-Ph]	F: 463 ; NMR1: 1.68-1.75(2H, m), 4.70(2H, d, J=5.3Hz), 8.53(1H,s)
81	Pre 13	CH_2-[3-HO$(CH_2)_3$-Ph]	F: 463 ; NMR1: 1.65-1.72(2H, m), 4.63(2H, d, J=5.9Hz), 8.51(1H,s)
82	Pre 13	CH_2-[2-HO$(CH_2)_2$-Ph]	F: 449 ; NMR1: 2.82(2H, t, J=7.3Hz), 6.80(2H, d, J=8.8Hz), 8.52(1H,s)
83	Pre 13	CH_2-[3-HO$(CH_2)_2$-Ph]	F: 449 ; NMR1: 2.70(2H, t, J=7.0Hz), 6.82(2H, d, J=9.3Hz), 8.51(1H,s)
84	Pre 13	CH_2-(2-MeS-Ph)	F: 451 ; NMR1: 3.73-3.78(4H, m), 4.67(2H, d, J=5.3Hz), 7.26-7.39(m, 4H), 8.52(1H, s) Sal HCl
85	Pre 13	CH_2-(2,6-$(HO)_2$-Ph)	F: 437
86	Ex 3	CH_2-(2-MeSO_2-Ph)	F: 483
87	Pre 13	CH_2[3-HO$(CH_2)_2$N(Me)-Ph]	F: 478 ; NMR1: 2.87(3H, s), 3.70-3.75(4H, m), 4.57(2H, d, J=5.8Hz), 8.50(1H, s) Sal HCl
88	Pre 13	CH_2-(3-MeO-6-F-Ph)	F: 453 ; NMR1: 3.75-3.78(4H,m), 3.64(3H, s), 4.70(2H, d, J=5.4Hz), 8.55(1H,s)
89	Pre 13	CH_2-(3-EtO_2C-Ph)	F: 477
90	Pre 13	CH_2-[3-HO$(CH_2)_2$NH-Ph]	FN: 462 ; NMR1: 3.70-3.75(4H, m), 4.54(2H, d, J=5.9Hz), 8.55(1H, s)
91	Pre 13	CH_2-(2-MeO-5-F-Ph)	F: 453 ; NMR1: 3.71-3.75(4H, m), 3.85(3H, s), 4.60(2H, d, J=5.9Hz), 8.52(1H, s)
92	Pre 13	CH_2-(2,3,5-F_3-Ph)	F: 459 ; NMR1: 3.71-3.76(4H, m), 4.73(2H, d, J=5.9Hz), 7.35-7.47(m, 3H), 8.54(1H, s)
93	Ex 3	CH_2-(2-O_2N-Ph)	F:450 ; NMR1: 3.72-3.75(4H, m), 4.95(2H, d, J=5.9Hz), 8.14 (1H, d, J=7.8Hz), 8.51(1H, s)
94	Ex 7	CH_2-(2-H_2N-Ph)	F:420
95	Pre 13	CH_2-(3-Cl-Ph)	F: 439 ; NMR1: 3.70-3.75(4H, m), 4.65(2H, d, J=5.8Hz), 7.33-7.39(m, 2H), 8.52(1H, s)
96	Pre 13		F: 411 ; NMR1: 3.69-3.74(4H, m), 4.84(2H, d, J=5.9Hz), 7.36-7.40(m, 1H), 8.52(1H, s)
97	Pre 13		F: 445 ; NMR1: 3.70-3.75(4H, m), 4.74(2H, d, J=6.4Hz), 8.52(1H, s)
98	Pre 13		F: 445 ; NMR1: 3.70-3.75(4H, m), 4.79(2H, d, J=5.8Hz), 7.47-7.54(m, 3H), 8.54(1H, s)
99	Pre 13		F: 412

Table 9

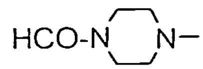
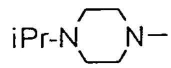
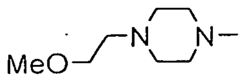
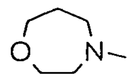
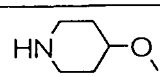
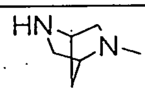
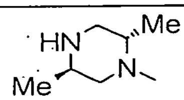
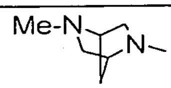
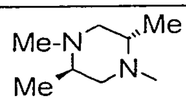
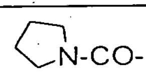
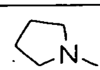
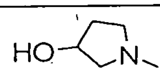
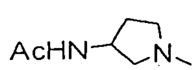
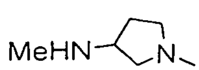
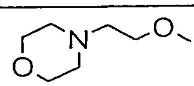
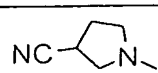
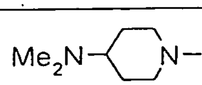
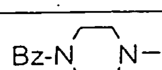


Ex	Syn	R^4	-Y-B	Dat
4	Ex 4		Bn	F: 433
5	Ex 5		Bn	F: 404
6	Ex 6		Bn	F: 433 ; NMR1: 4.20-4.26(1H, m), 4.66 (2H, d, J=5.8Hz), 8.53(1H, s)
9	Ex 9		Bn	F: 447
10	Ex 10		Bn	F: 512; NMR1: 2.94 (3H, s), 4.67 (2H, d, J=5.8Hz), 8.55 (1H, s) Sal: HCl
11	Ex 11		Bn	NMR1: 1.18(3H, t, J=7.2Hz), 4.66 (2H, d, J=6.0Hz), 8.51(1H,s)
12	Ex 12		Bn	F: 448 ; NMR1: 2.70-2.75 (1H, m), 4.68 (2H, d, J=5.8Hz), 8.61 (1H, s) Sal: 2HCl
13	Ex 13		Bn	F: 446 ; NMR1: 2.80-2.88(2H, m), 4.71 (2H, d, J=5.9Hz), 8.68(1H,s) Sal: 3HCl
14	Ex 14		Bn	F: 498
100	Ex 3		Bn	F: 433
101	Ex 3		Bn	F: 435
102	Ex 3		Bn	F: 417
103	Ex 3		Bn	F: 432 Sal: 3HCl
104	Ex 3		Bn	F: 467
105	Ex 3		Bn	F: 403 ; NMR1: 3.00-3.03 (4H, m), 4.66 (2H, d, J=5.9Hz), 8.51(1H, s)

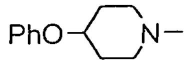
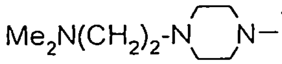
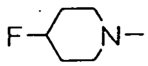
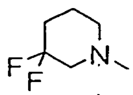
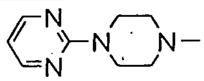
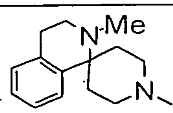
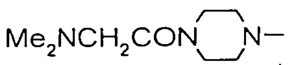
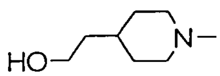
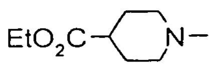
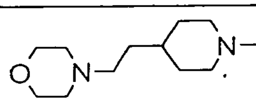
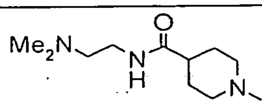
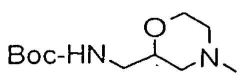
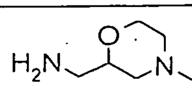
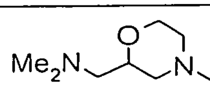
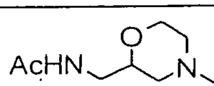
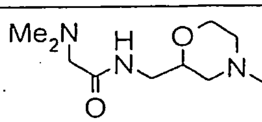
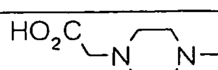
(Table 9 continued)

106	Ex 3		Bn	F: 431
107	Ex 3		Bn	F: 447 ; NMR1: 2.08(3H, s), 4.69(2H, d, J=5.8Hz), 8.55(1H, s)
108	Ex 3		Bn	F: 431 ; NMR1: 1.50(4H, br), 4.71 (2H, d, J=5.9Hz), 8.58(1H, s)
109	Ex 3		Bn	F: 467
110	Ex 3		Bn	F: 460
111	Ex 3		Bn	F: 445
112	Ex 3		Bn	F: 459
113	Ex 3		Bn	F: 453 ; NMR1: 3.66-3.68(4H, m), 4.67 (2H, d, J=5.9Hz), 8.52(1H, s)
114	Ex 3		Bn	F: 417 ; NMR1: 2.36(2H, t, J=6.3Hz), 4.69 (2H, d, J=5.9Hz), 8.56(1H, s)
115	Ex 3		Bn	F: 417
116	Ex 3		Bn	F: 418 ; NMR1: 2.24(3H, s), 4.66(2H, d, J=5.8Hz), 8.51(1H, s)
117	Ex 3		Bn	F: 433 ; NMR1: 3.65-3.72 2H, m), 4.67 (2H, d, J=6.3Hz), 8.52(1H, s)
118	Ex 3		Bn	F: 433 ; NMR1: 4.00-4.07(2H, m), 4.66 (2H, d, J=5.8Hz), 8.51(1H, s)
119	Ex 3		Bn	F: 433 ; NMR1: 3.49(4H, br), 4.71 (2H, d, J=5.8Hz), 8.58(1H, s)
120	Ex 3		Bn	F: 448
121	Ex 3		Bn	F: 462
122	Ex 3		Bn	F: 432
123	Ex 3		Bn	F: 419

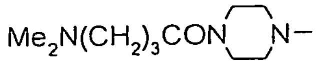
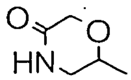
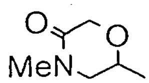
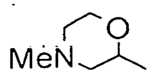
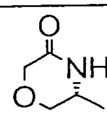
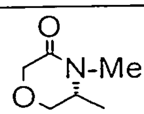
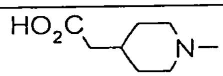
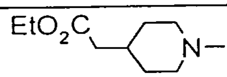
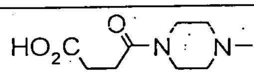
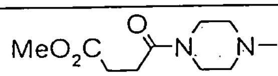
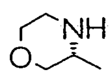
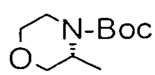
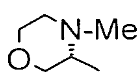
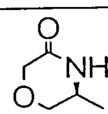
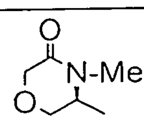
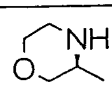
(Table 9 continued)

124	Ex 3		Bn	F: 432
125	Ex 3		Bn	F: 446 ; NMR1: 0.996(6H,d,J=6.4Hz), 4.66(2H, d, J=5.9Hz), 8.50(1H, s)
126	Ex 3		Bn	F: 462
127	Ex 3		Bn	F: 419 ; NMR1: 1.88(2H, quint, J=5.8 Hz), 4.65(2H, d, J=5.9Hz), 8.56(1H,s)
128	Ex 5		Bn	F: 419 ; NMR1: 4.34-4.40(1H, m), 4.66 (2H, d, J=5.9Hz), 8.53(1H, s)
129	Ex 5		Bn	FN: 414
130	Ex 5		Bn	F: 432
131	Ex 6		Bn	F: 430
132	Ex 6		Bn	F: 446
133	Pre 15		Bn	F: 417
134	Ex 3		Bn	F: 389 Sal HCl
135	Ex 3		Bn	F: 405 ; NMR1: 2.00-2.07(1H,m), 6.39(2H, d, J=8.8Hz), 8.48(1H,s)
136	Ex 3		Bn	F: 446 ; NMR1: 1.81(3H,s),4.30-4.40 (1H, m), 6.53(2H, d, J=7.8Hz) Sal: 2HCl
137	Ex 3		Bn	F: 418 ; NMR1:3.84-3.87(1H,m),4.67 (2H, d, J=5.6Hz),6.57(2H, d,J=8.3Hz) Sal: 2HCl
138	Ex 3		Bn	F: 449 ; NMR1: 3.70-3.75(4H, m), 4.68 (2H, d, J=5.9Hz), 8.64(1H, s) Sal: 2HCl
139	Ex 3		Bn	F: 414 ; NMR1: 2.17-2.15(1H, m), 4.65 (2H, d, J=5.9Hz), 8.50(1H,s)
140	Ex 3		Bn	F: 446 ; NMR1: 3.75-3.80(4H, m), 4.80 (2H, d, J=5.3Hz), 8.56(1H, s) Sal: 2HCl
141	Ex 3		Bn	F: 508 ; NMR1: 3.40-3.85(4H, m), 4.66 (2H, d, J=6.3Hz), 8.52(1H, s)

(Table 9 continued)

142	Ex 3		Bn	F: 495 Sal: HCl
142	Ex 3		Bn	F: 475 ; NMR1: 2.15(6H, s), 4.66(2H, d, J=5.9Hz), 8.51(1H,s)
144	Ex 3		Bn	F: 421 ; NMR1: 4.66(2H, d, J=5.4Hz), 4.70-4.90(1H, m), 8.51(1H, s)
145	Ex 3		Bn	F: 439 ; NMR1: 3.29-3.39(2H, m), 4.67 (2H, d, J=5.8Hz), 8.51(1H, s)
146	Ex 3		Bn	F: 482 ; NMR1: 3.29-3.39(2H, m), 4.67 (2H, d, J=5.8Hz), 8.51(1H, s) Sal: HCl
147	Ex 3		Bn	F: 534 ; NMR1: 3.64-3.72(2H, m), 4.71 (2H, d, J=6.3Hz), 8.61(1H, s) Sal: 3HCl
148	Ex 3		Bn	F: 489 ; NMR1: 2.83(6H, s), 4.68(2H, d, J=5.8Hz), 8.60(1H,s) Sal: 2HCl
149	Ex 3		Bn	F: 447 ; NMR1: 1.18-1.30(2H, m), 4.66(2H, d, J=5.9Hz), 8.51(1H,s)
150	Ex 3		Bn	NMR1: 1.19(3H, t, J=7.2Hz), 4.66(2H, d, J=6.0Hz), 8.51(1H,s)
151	Ex 3		Bn	F: 516 ; NMR1: 3.81-3.97(4H,m), 4.70 (2H, d, J=5.9Hz), 8.63(1H,s) Sal: 3HCl
152	Pre 4		Bn	F: 517 ; NMR1: 2.77(s,3H),3.13-3.17 (2H, m), 4.70(2H, d, J=6.4Hz) Sal: 3HCl
153	Ex 3		Bn	F: 534 ; NMR1: 1.39 (9H, s), 2.29 (1H, t, J=11.2Hz), 8.51 (1H, s)
154	Ex 5		Bn	F: 434 ; NMR1: 2.70-2.75 (1H, m), 4.68 (2H, d, J=5.8Hz), 8.61 (1H, s) Sal: 2HCl
155	Ex 6		Bn	F: 462 ; NMR1: 2.68-2.74 (1H, m), 4.67 (2H, d, J=5.9Hz), 8.52 (1H, s) Sal: 2HCl
156	Ex 8		Bn	F: 476 ; NMR1: 1.84 (3H, s), 2.41 (1H, t, J=11.3Hz), 8.53 (1H, s) Sal: HCl
157	Pre 4		Bn	F: 519 ; NMR1: 4.69 (2H, d,J=5.9Hz), 7.11 (2H, brd, J=6.8Hz), 8.69 (1H, s) Sal: 2HCl
158	Ex 9		Bn	F: 462 Sal: HCl

(Table 9 continued)

159	Pre 4		Bn	MP: 218-223 ; NMR1: 2.73(3H, s), 4.69(2H, d, J=5.8Hz) , 8.62(1H, s) Sal: 3HCl
160	Ex 3		Bn	F: 419 ; NMR1: 4.51-4.58(1H, m), 4.78(2H, d, J=5.8Hz), 8.57(1H, s)
161	Ex 3		Bn	F: 433 ; NMR1: 2.82(1.5H, s),2.89 (1.5H, s),4.70(2H, d, J=5.9Hz), 8.58 (0.5H, s), 8.60(0.5H, s) Sal: HCl
162	Ex 3		Bn	F: 419 ; NMR1: 2.74(3H, s),4.75(2H, d, J=6.4Hz), 8.61(1H, s) Sal: 2HCl
163	Ex 3		Bn	F: 419 ; NMR1: 4.58-4.62(1H, m), 4.71 (2H, d, J=5.8Hz), 8.61(1H, s) Sal: HCl
164	Ex 3		Bn	F: 433 ; NMR1: 2.69(3H, s),4.70(2H, d, J=5.8Hz), 8.61(1H, s) Sal: HCl
165	Ex 9		Bn	F: 461
166	Ex 3		Bn	NMR1:1.78-1.22(3H,m), 4.66(2h, d, J=6.0Hz), 8.51(1H,s)
167	Ex 9		Bn	F: 504
168	Ex 3		Bn	NMR1: 3.58(3H, s), 4.67(2H, d, J=4.0Hz), 8.51(1H,s)
169	Ex 5		Bn	F: 405 ; NMR1: 4.23-4.32(1H, m), 4.68-4.81 (2H, m), 8.65(1H, s) Sal: 2HCl
170	Ex 3		Bn	F: 505
171	Ex 6		Bn	F: 419 ; NMR1: 4.35-4.45(1H, m), 4.71 (2H, d, J=5.9Hz), 8.67(1H, s) Sal: 2HCl
172	Ex 3		Bn	F: 419 ; NMR1: 4.58-4.62(1H, m), 4.71 (2H, d, J=5.8Hz), 8.61(1H, s) Sal: HCl
173	Ex 3		Bn	F: 433 ; NMR1: 2.69(3H, s),4.70(2H, d, J=5.8Hz), 8.61(1H, s) Sal: HCl
174	Ex 5		Bn	F: 405 ; NMR1: 4.23-4.32(1H, m), 4.68-4.81(2H, m), 8.65(1H, s) Sal: 2HCl

(Table 9 continued)

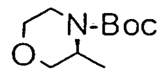
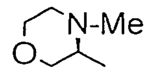
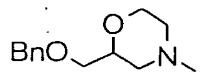
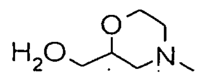
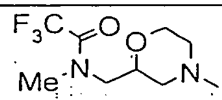
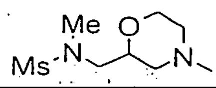
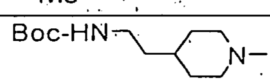
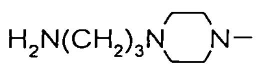
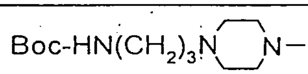
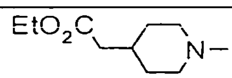
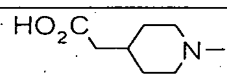
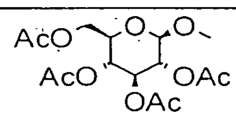
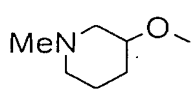
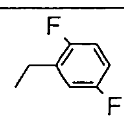
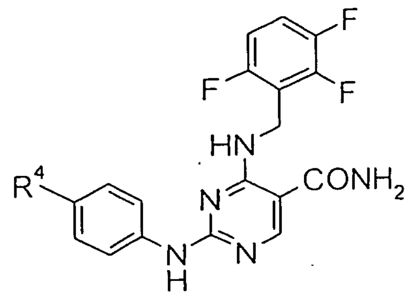
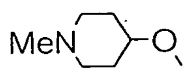
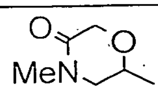
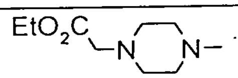
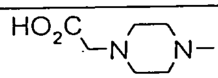
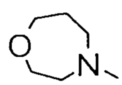
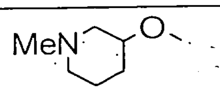
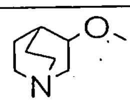
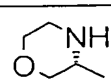
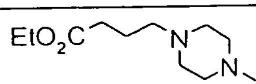
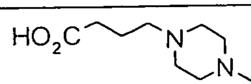
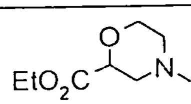
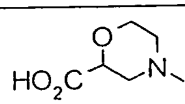
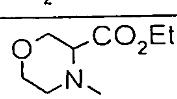
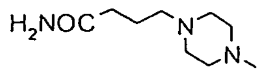
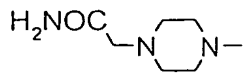
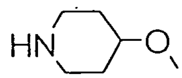
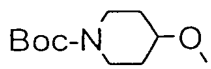
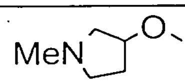
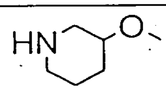
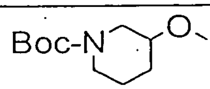
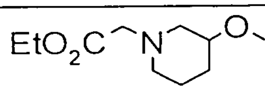
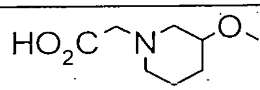
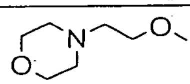
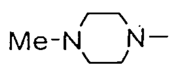
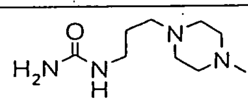
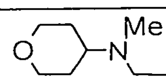
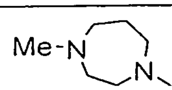
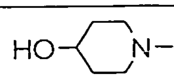
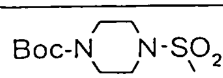
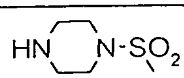
175	Ex 3		Bn	F: 505
176	Ex 6		Bn	F: 419 ; NMR1: 4.35-4.45(1H, m), 4.71(2H, d, J=5.9Hz), 8.67(1H, s) Sal: 2HCl
177	Ex 3		Bn	F: 525 ; NMR1: 2.70 (1H, br t, J=10.3 Hz), 4.53(2H, s), 8.53 (1H, s) Sal: HCl
178	Ex 7		Bn	F: 435 ; NMR1: 2.54-2.60 (1H, m), 4.68 (2H, d, J=5.9Hz), 8.57 (1H, s) Sal: HCl
179	Ex 3		Bn	F: 544 (ESI)
180	Ex 10		Bn	F: 526; NMR1: 2.86 (3H, s), 2.92 (3H, s), 8,55 (1H, s) Sal: HCl
181	Ex 3		Bn	F: 546
182	Ex 13		Bn	F: 461 NMR1: 2.06-2.33(2H,m), 4.68 (2H, d, J=5.9Hz), 8.60(1H,s) Sal: 3HCl
183	Ex 3		Bn	F: 561
184	Ex 3		Bn	F: 543 ; NMR1: 1.19(3H, t, J=7.1Hz), 4.82(2H, d, J=5.4Hz), 8.51(1H,s)
185	Ex 9		Bn	F: 515 ; NMR1: 2.19(2H, d, J=6.8Hz), 4.82(2H, d, J=5.9Hz), 8.51(1H, s)
186	Ex 3		Bn	F: 666
187	Ex 3			F: 469

Table 10

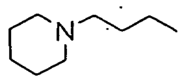
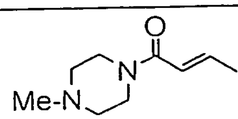
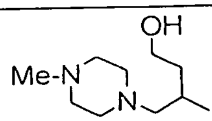
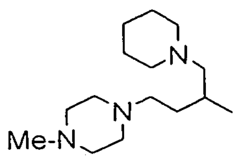
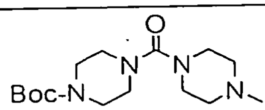
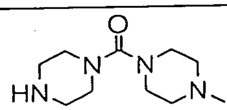
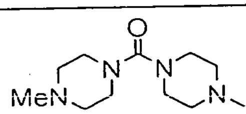
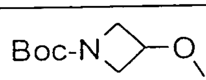
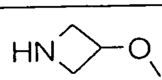
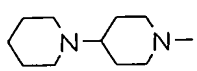
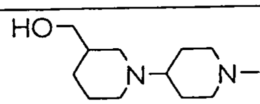
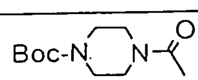
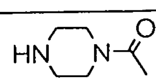
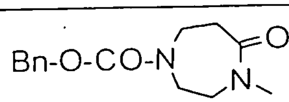


Ex	Syn	R^4	Dat
15	Ex 15		F: 487 ; NMR1: 2.17(3H,s), 4.82(2H, d, J=5.8Hz), 8.52(1H,s)
188	Ex 3		F: 487 ; NMR1: 2.90(3H, s),4.88(2H, d, J=5.9Hz), 8.63(1H, s) Sal: HCl
189	Ex 3		F: 544 ; NMR1: 1.20(3H, t, J=7.1Hz), 4.83(2H, d, J=5.4Hz), 8.52(1H, s)
190	Ex 9		F: 516 ; NMR1: 3.20(2H, s), 4.83(2H, d, J=5.9Hz), 8.52(1H,s)
191	Ex 3		F: 473 ; NMR1: 3.70-3.76(4H, m), 4.85(2H, d, J=5.9Hz), 8.52(1H, s) Sal: HCl
192	Ex 3		F: 487 ; NMR1: 2.78(3H, d, J=3.9Hz), 4.81-4.89 (2H, m), 8.64(1H, s) Sal: 2HCl
193	Ex 3		F: 499 ; NMR1: 3.72-3.81(1H, m), 4.85(2H, d, J=5.6Hz), 8.69(1H, s) Sal: 2HCl
194	Ex 5		F: 459 ; NMR1: 4.40-4.48(1H, m), 4.88 (2H, d, J=5.4Hz), 8.69(1H, s) Sal: 2HCl
195	Ex 3		F: 572
196	Ex 9		F: 544
197	Ex 3		F: 531
198	Ex 9		F: 503
199	Ex 3		F: 531 NMR1: 4.59-4.64(1H, m), 4.84(2H, d, J=5.8Hz), 8.52(1H, s) Sal: HCl

(Table 10 continued)

200	Ex 3		F: 543 NMR1: 1.63-1.70(2H, m), 4.83(2H, d, J=5.9Hz), 8.51(1H, s)
201	Ex 3		F: 515 NMR1: 4.02(2H, s), 4.86(2H, d, J=5.9Hz), 8.67(1H, s) Sal: 2HCl
202	Ex 13		F: 473 ; NMR1: 4.25-4.32(1H, m), 4.83(2H, d, J=5.9Hz), 8.53(1H, s)
203	Ex 3		F: 573
204	Ex 3		F: 473 ; NMR1: 2.27(3H, s), 4.82(2H, d, J=5.3Hz), 8.52(1H, s)
205	Ex 13		F: 473 ; NMR1: 4.11-4.16(1H, m), 4.82(2H, d, J=5.9Hz), 8.53(1H, s)
206	Ex 3		NMR2: 1.42(9H, s), 4.83(2H, d, J=5.6Hz), 8.24(1H, s)
207	Ex 11		F: 559 ; NMR1: 1.17(3H, t, =7.1Hz), 4.82(2H, d, J=5.8Hz), 8.52(1H, s)
208	Ex 9		F: 531 ; NMR1: 1.17-1.98(4H, m), 4.83(2H, d, J=5.9Hz), 8.54(1H, S)
209	Ex 3		F: 503 ; NMR1: 4.42-4.44 (2H, m), 4.85 (2H, d, J=5.9Hz), 8.58 (1H, s) Sal: 2HCl
210	Ex 3		F: 472 ; NMR1: 4.85 (2H, d, J=5.9Hz) 7.01 (2H, d, J=9.2Hz), 8.57 (1H, s) Sal: 2HCl
211	Ex 3		F: 558 ; NMR1: 1.51-1.58(2H, m), 4.82(2H, d, J=5.9Hz), 8.51(1H, s)
212	Ex 3		F: 501 ; NMR1: 2.10 (3H, s), 3.49 (2H, s), 8.55 (1H, s)
213	Ex 3		F: 486 ; NMR1: 4.85 (2H, d,J=5.8Hz), 6.78 (2H, d, J=8.3Hz), 8.57 (1H, br s) Sal: 2HCl
214	Ex 3		F: 473 Sal: HCl
215	Ex 3		ESI: 622
216	Ex 5		F: 522

(Table 10 continued)

217	Ex 3		F: 499 ; NMR1: 1.34-1.40 (1H,m), 2.96-3.01 (2H,m), 4.88 (2H, d, J=5.8Hz), 8.67 (1H, s) Sal: 2HCl
218	Ex 3		F: 526 Sal: 2HCl
219	Ex 3		F: 544 Sal: 2.9HCl
220	Ex 3		F: 611 Sal: 3.7HCl
221	Ex 3		ESI: 670
222	Ex 5		F: 570 ; NMR1: 3.04-3.13(4H, m), 4.86(2H, d, J=5.8Hz), 7.44-7.56(4H, m), 8.65(1H, s) Sal: 3HCl
223	Ex 6		F: 584 ; NMR1: 2.75(3H, d, J=4.3Hz), 2.95-3.07(2H, m), 4.86(2H, d, J=5.9Hz), 8.61(1H, s) Sal: 2HCl
224	Ex 3		F: 545
225	Ex 5		F: 445 ; NMR1: 3.93-4.03(2H, m), 4.83(2H, d, J=5.8Hz), 5.03-5.11(1H, m), 8.59(1H, s) Sal: 2HCl
226	Ex 6		F: 459 ; NMR1: 3.98-4.07(1H, m), 4.83(2H, d, J=5.9Hz), 4.93-5.01(0.5H, m), 5.13-5.20(0.5H, m), 8.62(1H, s) Sal: 2HCl
227	Ex 3		F: 540 ; NMR1: 1.70-2.29 (7H,m), 3.50 (2H, d, J=11.1Hz), 4.86 (2H, d, J=5.8Hz), 8.64 (1H, s) Sal: 3HCl
228	Ex 3		F: 570 Sal: 2HCl
229	Ex 3		ESI: 586
230	Ex 5		F: 486 Sal: 2HCl
231	Ex 3		ESI: 620

(Table 10 continued)

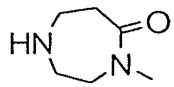
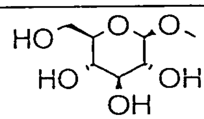
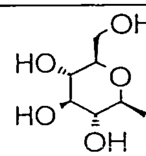
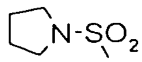
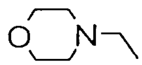
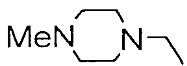
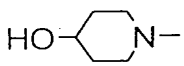
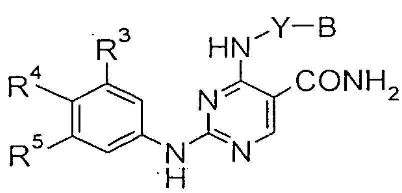
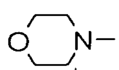
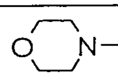
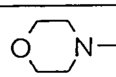
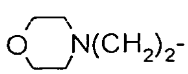
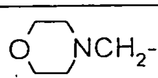
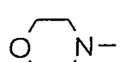
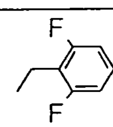
232	Ex 7		F: 486 ; NMR1: 2.94-2.96 (2H,br d), 4.03 (2H, br), 7.48-7.52 (1H,m), 8.60 (1H, s) Sal: 2HCl
233	Ex 14		F: 552 ; NMR1: 4.83(2H, d,J=5.8Hz), 5.25-5.30(1H, m),8.53(1H, s)
234	Ex 14		F: 536
235	Pre 15		ESI: 507
236	Pre 15		ESI: 473
237	Pre 15		ESI: 486
238	Pre 15		ESI: 473

Table 11



Ex	Syn	R^3	R^4	R^5	-Y-B	Dat
239	Ex 3	H		F	Bn	F: 423 ; NMR1: 4.69(2H, d, J= 6.4Hz), 6.90(1H, t, J=9.3Hz), 8.55(1H, s)
240	Ex 3	H		F_3C	Bn	F: 473
241	Ex 3		H	H	Bn	F: 405
242	Ex 3		H	H	Bn	F: 433 ; NMR1: 2.41-2.45 (2H, m), 4.72(2H, d, J=5.9 Hz), 8.62(1H, s)
243	Ex 3		H	H	Bn	F: 419
244	Ex 3	H		F		F: 459 ; NMR1: 4.81(2H, d, J= 5.4Hz), 6.95-7.00(1H, m), 8.55(1H, s)

(Table 11 continued)

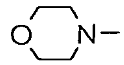
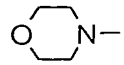
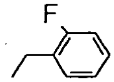
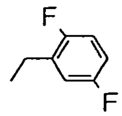
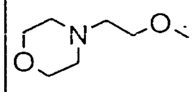
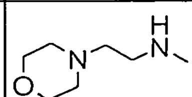
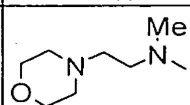
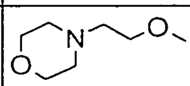
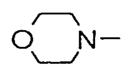
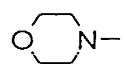
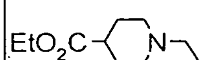
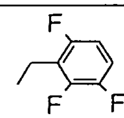
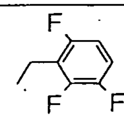
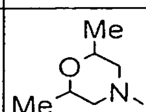
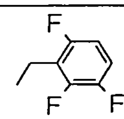
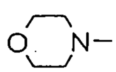
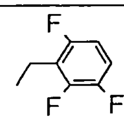
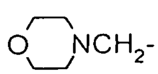
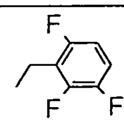
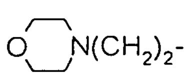
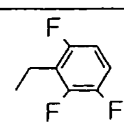
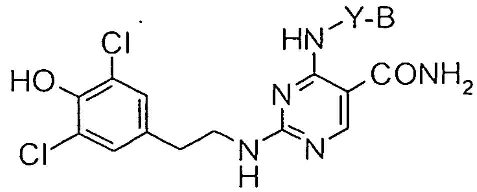
245	Ex 3	F		F	Bn	F: 441
246	Ex 3	F		H		F: 441 ; NMR1 2.91-2.93(4H, m), 4.75(2H, d, J=5.8Hz), 8.57(1H, s,)
247	Ex 3	F		H		F: 459 ; NMR1: 4.72(2H, d, J= 6.1Hz), 6.86-6.90(1H, m), 8.57(1H, s)
248	Ex 3		H	H	Bn	F: 449 ; NMR1 4.35-4.42(2H, m),4.75(2H, d, J=6.4Hz), 8.69(1H, s) Sal: 2HCl
249	Ex 3		H	H	Bn	F: 448 ; NMR1: 3.37-3.47 (4H, m),4.73(2H, d, J=5.8 Hz), 8.56(1H, s) Sal: 2HCl
250	Ex 3		H	H	Bn	F: 462 ; NMR1: 2.85(3H, s), 4.74(2H, d, J=5.8Hz), 8.64 (1H, s) Sal: 2HCl
251	Ex 3			H	Bn	F: 534 ; NMR1: 3.67-3.71 (4H, s),4.72(2H, d, J=5.9Hz), 8.54(1H, s)
252	Ex 3	$HOCH_2$-		H	Bn	F: 435 ; NMR1: 4.53(2H, s), 4.71(2H, d, J=5.9Hz), 8.53 (1H, s)
253	Pre 15		H	H		ESI: 543
254	Pre 15	Et_2NCH_2-	H	H		ESI: 459
255	Pre 15	HO_2C-		H		ESI: 531
256	Pre 15		H	H		ESI: 459
257	Pre 15		H	H		ESI: 473
258	Ex 3		H	H		F: 487 ; NMR1:3.09-3.14(4H, m), 3.81-3.87 (2H,m), 4.89 (2H, d, J=5.9Hz), 8.68(1H, s) Sal: 2HCl

Table 12



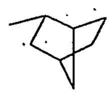
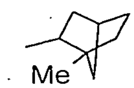
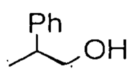
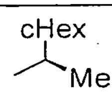
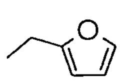
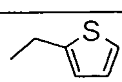
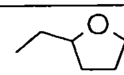
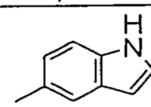
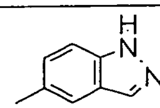
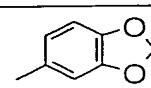
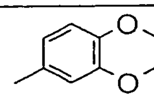
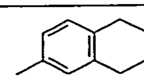
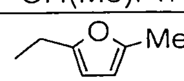
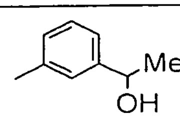
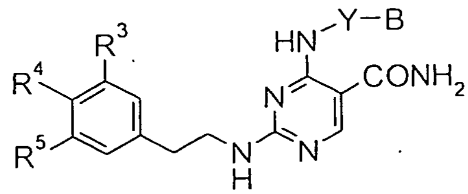
Pre	Syn	-Y-B	Dat
16	—	4-Me-cHex	F: 438
17	—	cBu	F: 396
18	—	cPen	F: 410
19	—		F: 436
20	—		F: 478
21	—		F: 462
22	—		F: 452
23	—	cHep	F: 438
24	—	cOct	F: 452
25	—	2Ad	F: 476
26	—	CH_2-(2-Cl-Ph)	F: 466
27	—	CH_2-(2-Br-Ph)	F: 510
28	—	CH_2-(2,6-F_2-Ph)	F: 468
29	—	CH_2-(3-F-Ph)	F: 450
30	—	CH_2-(3-Cl-Ph)	F: 466
31	—	CH_2-(2,6-F_2-Ph)	F: 468
32	—		F: 422
33	—		F: 438
34	—		F: 426
35	—	CH_2-tBu	F: 412
36	—	$(CH_2)_2CHMe_2$	F: 412
37	—		F: 457
38	—		F: 458
39	—		F: 462
40	—		F: 476
41	—		F: 472
42	—	3-HO-Ph	F: 434
43	—	4-MeO-Ph	F: 448
44	—	CH_2-(2-F_3C-Ph)	F: 500
45	—	CH_2-(2-MeO-Ph)	F: 462
94	Ex 1	cHex	F: 424
95	Pre 3	CH_2CHMe_2	F: 398
96	Pre 3	CH(Me)Ph	F: 446
97	Pre 3		F: 436
98	Pre 4		F: 462

Table 13



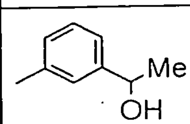
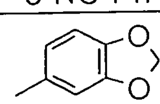
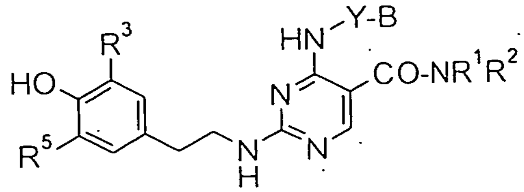
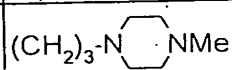
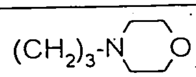
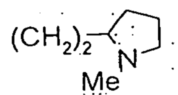
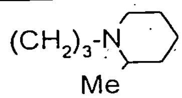
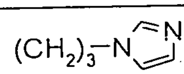
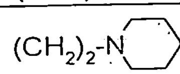
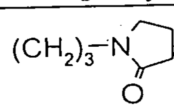
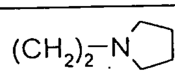
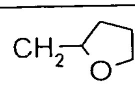
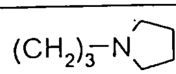
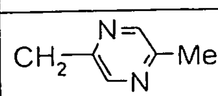
Pre	Syn	R^3	R^4	R^5	-Y-B	Dat
1	Pre 1	Br	HO	H	3-Me-Ph	F: 443 ; NMR1:2.75(2H,t,J=7.3 Hz), 8.55(0.8H,s),8.61(0.2H,s),9.99(1H,s)
2	Pre 2	Cl	HO	H	3-Et-Ph	F: 412
58	—	Cl	HO	H	3Qui	F: 435
59	—	Cl	HO	H	2-Me-Ph	F: 398
60	—	Cl	HO	H	3-iPr-Ph	F: 426
61	—	Cl	HO	H	3-$HOCH_2$-Ph	F: 414
62	—	Cl	HO	H	3-MeS-Ph	F: 430
63	—	Cl	HO	H	4-Me-Ph	F: 398
64	—	Cl	HO	H	3,5-Me_2-Ph	F: 412
65	—	Cl	HO	H	3,5-Cl_2-Ph	F: 453
66	—	Cl	HO	H	3-Ac-Ph	F: 426
67	—	Cl	HO	H	4-F-3-Me-Ph	F: 416
68	—	Cl	HO	H	2,4-F_2-Ph	F: 420
69	—	Cl	HO	H	CH_2-(3-Me-Ph)	F: 412
99	Pre 1	Cl	HO	H	3-Me-Ph	F: 398 ; NMR1: 2.75(2H,t,J=6.9Hz), 8.55(0.7H,s),8.61(0.3H,s),9.91(1H,s)
100	Pre 1	H	AcNH	H	3-Me-Ph	F: 405
101	Pre 1	HO	H	H	3-Me-Ph	F: 364
102	Pre 1	H	$MeSO_2NH$	H	3-Me-Ph	F: 441
103	Pre 1	H	HCOHN	H	3-Me-Ph	F: 391
104	Pre 1	F	HO	H	3-Me-Ph	F: 382 ; NMR1:2.75(2H,t,J=7.3 Hz), 8.55(0.7H,s),8.61(0.3H,s),9.58(1H,s)
105	Pre 1	MeO	HO	H	3-Me-Ph	F: 394
106	Pre 1	Me	HO	H	3-Me-Ph	F: 378
107	Pre 1	MeO	HO	MeO	3-Me-Ph	F: 424
108	Pre 1	Cl	HO	Cl	3-Me-Ph	F: 432 ; NMR1:2.77(2H,t,J=7.3Hz), 8.55(0.7H,s),8.61(0.3H,s),9.88(1H,s)
109	Pre 1	Cl	HO	H		F: 428 ; NMR1: 5.12(1H, d, J=3.9 Hz), 8.54(0.7H, s), 8.61(0.3H, s), 9.90(1H, s)
110	Pre 2	Cl	HO	H	3-NC-Ph	F: 409
111	Pre 2	Cl	HO	H		F: 428
112	Ex 1	Cl	HO	H	cHex	F: 390

Table 14



Pre	Syn	R^3	R^5	R^1	R^2	-Y-B	Dat
4	Pre 4	H	H	$(CH_2)_2NMe_2$	H	3-Me-Ph	F: 435
74	—	H	H		H	3-Me-Ph	F: 504
75	—	H	H		H	3-Me-Ph	F: 491
76	—	H	H	$(CH_2)_2OMe$	H	3-Me-Ph	F: 422
77	—	H	H		H	3-Me-Ph	F: 475
78	—	H	H	$(CH_2)_3NMe_2$	H	3-Me-Ph	F: 449
79	—	H	H	$(CH_2)_3OMe$	H	3-Me-Ph	F: 436
80	—	H	H		H	3-Me-Ph	F: 503
81	—	H	H		H	3-Me-Ph	F: 472
82	—	H	H	OMe	H	3-Me-Ph	F: 394
83	—	H	H	$(CH_2)_3NMe_2$	H	3-Me-Ph	F: 463
84	—	H	H		H	3-Me-Ph	F: 475
85	—	H	H	$(CH_2)_2$-3Py	H	3-Me-Ph	F: 469
86	—	H	H	CH_2-3Py	H	3-Me-Ph	F: 455
87	—	H	H		H	3-Me-Ph	F: 489
88	—	H	H		H	3-Me-Ph	F: 461
89	—	H	H		H	3-Me-Ph	F: 448
90	—	H	H		H	3-Me-Ph	F: 475
91	—	H	H		H	3-Me-Ph	F: 470
92	—	H	H	$(CH_2)_2SMe$	H	3-Me-Ph	F: 438

(Table 14 continued)

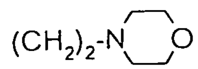
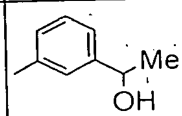
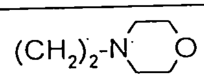
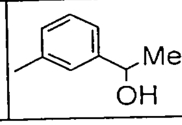
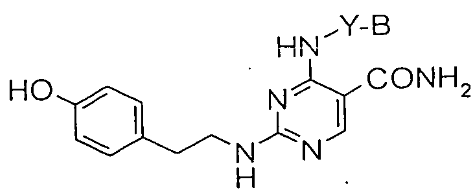
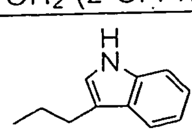
93	—	H	H	CH_2-2Py	H	3-Me-Ph	F: 455
113	Ex 2	H	H	Me	H	3-Me-Ph	F: 378
114	Ex 2	H	H	Me	Me	3-Me-Ph	F: 392
115	Ex 2	H	H	Et	H	3-Me-Ph	F: 392
116	Ex 2	H	H	^{i}Pr	H	3-Me-Ph	F: 406
117	Ex 2	H	H		H	3-Me-Ph	F: 477
118	Ex 2	H	H	$(CH_2)_2OH$	H	3-Me-Ph	F: 408
119	Ex 2	Cl	H	Me	H	3-Me-Ph	F: 412
120	Pre 4	Cl	Cl	Me	H		F: 476 ; NMR1: 1.30(3H, d, J=6.3Hz), 2.76-2.80 (5H, m), 8.65(1H, s) Sal: HCl
121	Ex 2	Cl	Cl		H	3-Me-Ph	F: 511 Sal: 2HCl
122	Pre 4	Cl	Cl	$(CH_2)_2OH$	H		F: 506 Sal: HCl

Table 15



Pre	Syn	-Y-B	Dat
3	Pre 3	-cHex	F: 356
46	—	$-CH_2-(2,6-F_2-Ph)$	F: 400
47	—	$-CH_2$-(2-MeO-Ph)	F: 394
48	—	$-CH_2$-tBu	F: 344
49	—	$-(CH_2)_2-CHMe_2$	F: 344
50	—	-cPen	F: 342
51	—	$-CH_2$-2Py	F: 365
52	—	$-CH_2$-(2-Cl-Ph)	F: 398
54	—		F: 417
53	—	$-CH_2$-(3-Me-Ph)	F: 378
55	—	$-(CH_2)_2$-SEt	F: 362

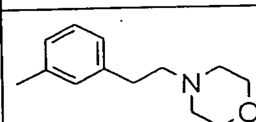
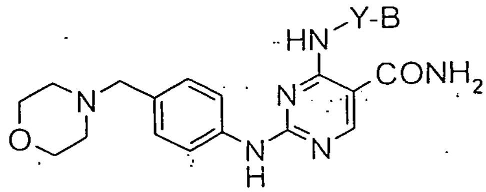
Pre	Syn	-Y-B	Dat
56	—	$-CH_2-(3,5-F_2-Ph)$	F: 400
57	—	$-CH_2-(2,3-Cl_2-Ph)$	F: 433
70	—	-(2-Me-Ph)	F: 364
71	—	-(3-MeS-Ph)	F: 396
72	—	-(4-Me-Ph)	F: 364
73	—	$-(3,5-Me_2-Ph)$	F: 378
123	Pre 3	-Ph	F: 350
124	Pre 3	-Bn	F: 364
125	Pre 3		F: 463 Sal: 2HCl
126	Pre 3	$-CH_2$-cHex	F: 370

Table 16



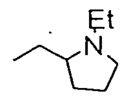
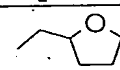
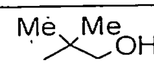
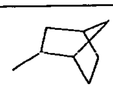
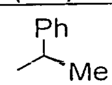
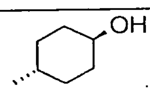
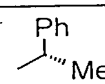
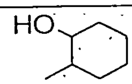
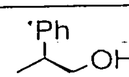
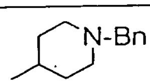
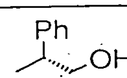
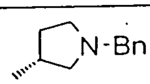
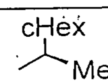
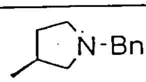
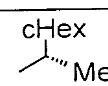
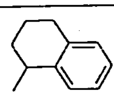
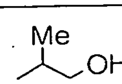
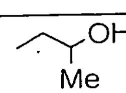
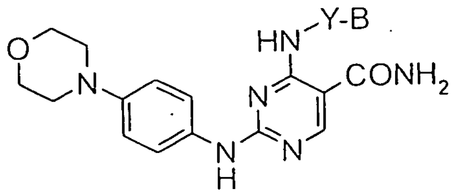
Pre	Syn	-Y-B	Dat	Pre	Syn	-Y-B	Dat
13	Pre 13	iPr	F: 371 ; NMR1: 3.00-3.03 (6H,d, J=6.8Hz), 3.55-3.57(4H, m), 8.50(1H, s)	143	Pre 14		F: 440
14	Pre 14	cPr	F: 369	144	Pre 14	CH_2-CH=CH_2	F: 369
127	Pre 13	CH_2-iPr	F: 385	145	Pre 14	CH_2-C≡CH	F: 367
128	Pre 13	tBu	F: 385 Sal: 2HCl	146	Pre 14		F: 413
129	Ex 3	3-Me-Ph	F: 419 Sal: 2HCl	147	Pre 14		F: 401
130	Pre 14	cPen	F: 397	148	Pre 14	CH_2CF_3	F: 411
131	Pre 14	cHex	F: 411	149	Pre 14	CH_2-cPr	F: 383
132	Pre 14	cHep	F: 425	150	Pre 14	$(CH_2)_2$Ph	F: 433
133	Pre 14	cOct	F: 439	151	Pre 14	$C(Me)_2$Ph	F: 447
134	Pre 14		F: 423	152	Pre 14		F: 433
135	Pre 14		F: 427	153	Pre 14		F: 433
136	Pre 14		F: 427	154	Pre 14		F: 449
137	Pre 14		F: 502	155	Pre 14		F: 449
138	Pre 14		F: 488	156	Pre 14		F: 439
139	Pre 14		F: 488	157	Pre 14		F: 439
140	Pre 14		F: 459	158	Pre 14		F: 387
141	Pre 14	$(CH_2)_2$OMe	F: 387	159	Pre 14		F: 387
142	Pre 14	CH_2-CN	F: 368				

Table 17



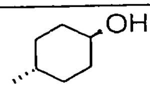
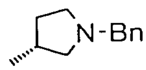
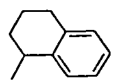
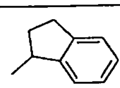
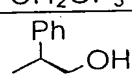
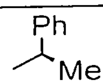
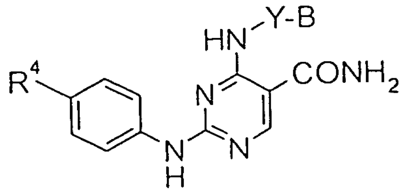
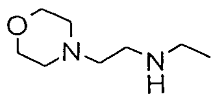
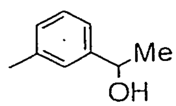
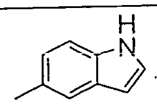
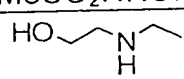
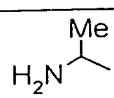
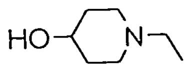
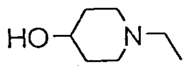
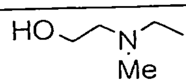
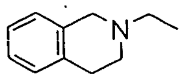
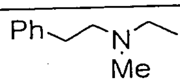
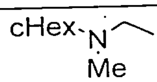
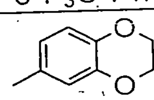
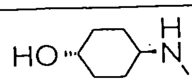
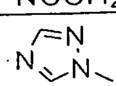
Pre	Syn	-Y-B	Dat
12	Pre 12	cHex	F: 397 ; NMR1: 1.95-1.98(2H, m), 3.02-3.04(4H, m), 8.47(1H, s)
160	Pre 13		F: 413
161	Pre 13		F: 475
162	Pre 13		F: 445 ; NMR1: 2.97-3.03(m, 4H), 5.36-5.44(m, 1H), 8.56(s, 1H)
163	Pre 13		F: 431 ; NMR1: 2.96-3.06(m, 4H), 5.60-5.70(m, 1H), 8.54(s, 1H)
164	Pre 13	$C(Me)_2$-Ph	F: 433 ; NMR1: 1.67(6H, s), 2.94-3.02(4H, m), 8.49 (1H, s)
165	Pre 13	CH(Me)-(2-F-Ph)	F: 437 ; NMR1: 8.52 (1H,s), 3.73-3.76 (4H, m), 1.49 (3H, d, J=6.9Hz)
166	Pre 13	CH(2-F-Ph)-CH_2OH	F: 453 ; NMR1: 5.13-5.16(1H, m), 6.78(2H, d, J=9.3Hz), 8.51(1H,s)
167	Ex 3	3-Me-Ph	F: 405 Sal: HCl
168	Ex 3	3-F_3C-Ph	F: 459
169	Ex 3	CH_2CF_3	F: 397
170	Ex 3		F: 435
171	Ex 3		F: 419
172	Pre 13	CH(Me)-(2-F-Ph)	F: 437;NMR1: 1.49(3H, d, J=6.9Hz), 6.79(2H, d, J=9.1HZ), 8.52(1H,s)
173	Pre 13	$(CH_2)_2$-Ph	F: 419 ; NMR1: 3.62-3.70(2H, m), 3.72-3.76(4H, m), 8.48(1H, s)

Table 18



Pre	Syn	R^4	-Y-B	Dat
5	Pre 5	$AcNHCH_2$	3-Me-Ph	F: 391
6	Pre 6	$H_2NCONHCH_2$	3-Me-Ph	F: 392
7	Pre 7	$MeNHCH_2$	3-Me-Ph	F: 363
8	Pre 8		3-Me-Ph	F: 462 Sal: 3HCl
9	Pre 9	Me_2NCH_2	3-Me-Ph	F: 377 Sal: 2HCl
10	Pre 10	$HO(CH_2)_2$	3-Me-Ph	F: 364
11	Pre 11	MeO	Bn	F: 350
15	Pre 15	H	Bn	F: 320
174	Pre 4	$HO(CH_2)_2$		F: 394
175	Pre 4	$HO(CH_2)_2$		F: 389
176	Pre 4	$HO(CH_2)_2$	3,5-F_2-Ph	F: 386
177	Pre 4	$HO(CH_2)_2$	2,5-F_2-Ph	F: 386 ; NMR1: 2.70(2H, t, J=7.3Hz), 6.84-6.90(1H, m), 8.77(1H, s)
178	Pre 4	$HO(CH_2)_2$	2,6-F_2-Ph	F: 386
179	Pre 4	$HO(CH_2)_2$	3,4-F_2-Ph	F: 386
180	Pre 4	$HO(CH_2)_2$	2,4-F_2-Ph	F: 386 ; NMR1: 2.68(2H, t, J=7.3Hz), 7.03-7.07(1H, m), 8.72(1H, s)
181	Pre 5	$MeSO_2NHCH_2$	3-Me-Ph	F: 427
182	Pre 8		3-Me-Ph	F: 393 Sal: 2HCl
183	Pre 8		3-Me-Ph	F: 363 ; NMR1: 1.52 (3H, d, J=6.8Hz), 2.32(3H, s), 8.86(1H, s) Sal: 2HCl
184	Pre 10	$HOCH_2$	3-Me-Ph	F: 350
185	Pre 10	HO	3-Me-Ph	F: 336
186	Pre 10	4-OH-Ph	3-Me-Ph	F: 412
187	Pre 10	Et	3-Me-Ph	F: 348
188	Ex 3	Et_2NCO	3-Me-Ph	F: 419 Sal: HCl
189	Ex 3	Me_2NCH_2	Bn	F: 377

(Table 18 continued)

190	Ex 3	$HO(CH_2)_2$	Bn	F: 364 Sal: HCl
191	Ex 3		3-Me-Ph	F: 433 Sal: 2HCl
192	Ex 3		3-NC-Ph	F: 444
193	Ex 3		Bn	F: 407 Sal: 2HCl
194	Ex 3		Bn	F: 465
195	Ex 3		Bn	F: 467
196	Ex 3		Bn	F: 445 Sal: 2HCl
197	Ex 3	$(HOCH_2)_2CH$	Bn	F: 394
198	Ex 3	$HO(CH_2)_3$	Bn	F: 378
199	Ex 3	$HO(CH_2)_2$	3-Et-Ph	F: 378
200	Ex 3	$HOC(CF_3)_2$	Bn	F: 486 Sal: HCl
201	Ex 3	$HO(CH_2)_2$	3-NC-Ph	F: 375
202	Ex 3	$HO(CH_2)_2$	$3\text{-}F_3C\text{-}Ph$	F: 418
203	Ex 3	$HO(CH_2)_2$		F: 408
204	Ex 3	$HOCH_2CMe_2$	3-Me-Ph	F: 392 ; NMR1: 1.22(6H, s), 2.30(3H, s), 8.70(1H, s)
205	Ex 3	$MeO(CH_2)_2$	3-Me-Ph	F: 378
206	Ex 3	$HOCH_2C(Me)_2$	Bn	F: 392 ; NMR1: 1.19(6H, s), 4.69(2H, d, J=5.8Hz), 8.54(1H, s)
207	Ex 3		$CH_2\text{-}(2,3,6\text{-}F_3\text{-}Ph)$	F: 487 ; NMR1: 4.04-4.12(1H, m), 4.52(1H, d, J=4.4Hz), 4.81(2H, d, J=5.9Hz), 8.48(1H, s)
208	Pre 15	Me_2N	Bn	F: 363
209	Pre 15	Et_2N	Bn	F: 391
210	Pre 15	MeS	Bn	F: 366
211	Pre 15	AcHN	Bn	F: 377
212	Pre 15	EtO_2CCH_2	Bn	F: 406
213	Pre 15	$NCCH_2$	Bn	F: 359
214	Pre 15		Bn	F: 387
215	Pre 15	HO	Bn	F: 336
216	Pre 15	$MeSO_2$	Bn	F: 398
217	Pre 15	Ac	$CH_2\text{-}(2,3,6\text{-}F_3\text{-}Ph)$	ESI: 416
218	Pre 15	$CH_3(CH_2)_3O\text{-}$	$CH_2\text{-}(2,3,6\text{-}F_3\text{-}Ph)$	ESI: 446

(Table 18 continued)

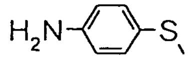
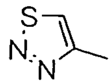
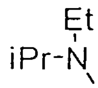
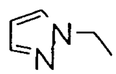
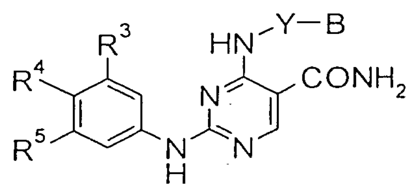
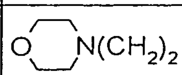
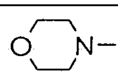
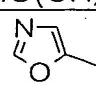
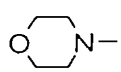
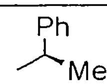
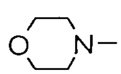
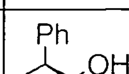
219	Pre 15		CH_2-(2,3,6-F_3-Ph)	ESI: 497
220	Pre 15		CH_2-(2,3,6-F_3-Ph)	ESI: 458
221	Pre 15	Ph-HN-	CH_2-(2,3,6-F_3-Ph)	ESI: 465
222	Pre 15		CH_2-(2,3,6-F_3-Ph)	ESI: 459
223	Pre 15	BnO-CONH-	CH_2-(2,3,6-F_3-Ph)	ESI: 537
224	Pre 15		CH_2-(2,3,6-F_3-Ph)	ESI: 454
225	Pre 15	AcN(Me)-	CH_2-(2,3,6-F_3-Ph)	ESI: 445
226	Pre 15	EtO-	CH_2-(2,3,6-F_3-Ph)	ESI: 418

Table 19



Pre	Syn	R^3	R^4	R^5	-Y-B	Dat
227	Ex 3		H	H	3-Me-Ph	F: 433
228	Ex 3		H	H	3-Me-Ph	F: 405
229	Ex 3	H	$HO(CH_2)_2$	F	Bn	F: 382
230	Ex 3	H		MeO	Bn	F: 417
231	Ex 3	F		H		F: 437 ; NMR1: 1.50(3H, d, J=6.9Hz), 2.93-2.95(4H, m), 8.54(1H, s)
232	Ex 3	F		H		F: 453 ; NMR1: 2.93-2.95 (4H, m), 5.07-5.09(1H, m), 8.53(1H, s)
233	Pre 15	MeO	H	H	Bn	F: 350
234	Pre 15	Ac	H	H	Bn	F: 362
235	Pre 15	HO	H	H	Bn	F: 336
236	Pre 15	$HOCH_2$	H	H	Bn	F: 350
237	Pre 15	MeS	H	H	Bn	F: 366
238	Pre 15	MeO	MeO	H	Bn	F: 380
239	Pre 15	Cl	HO	H	Bn	F: 370

(Table 19 continued)

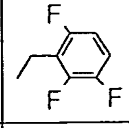
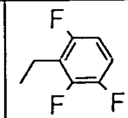
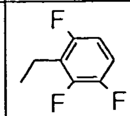
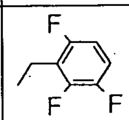
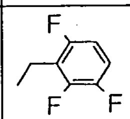
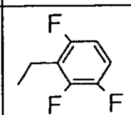
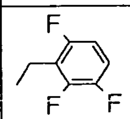
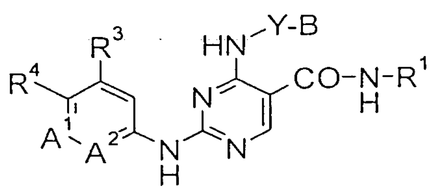
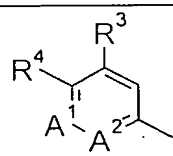
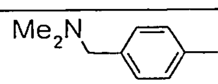
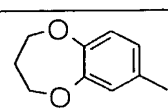
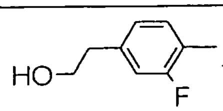
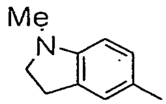
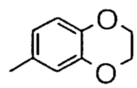
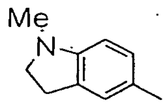
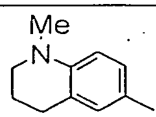
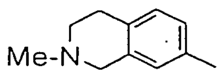
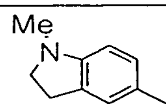
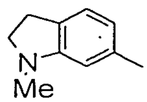
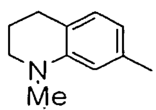
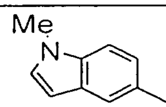
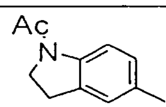
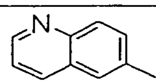
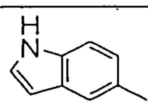
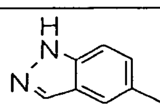
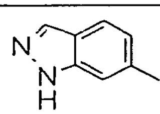
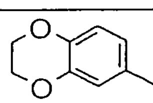
240	Pre 15	Et_2NCH_2-	HO-	H		ESI: 475
241	Pre 15	Cl	MeO-	H		ESI: 438
242	Pre 15	BuNH-SO_2-	H	H		ESI: 509
243	Pre 15	F	MeO-	H		ESI: 422
244	Pre 15	HO-CH(Me)-	H	H		ESI: 418
245	Pre 15	BnOCONH-	H	H		ESI: 537
246	Pre 15	HOH_2C-	HO-	H		ESI: 420

Table 20



Pre	Syn	R^1		-Y-B	Dat
247	Pre 9	Me		3-Me-Ph	F: 391
248	Pre 11	H		Bn	F: 392
249	Ex 3	H		Bn	F: 382

(Table 20 continued)

250	Ex 3	H			FN: 417
251	Ex 3	H		CH_2-(2-F-Ph)	FN: 393 ; NMR1: 2.64(3H, s), 4.71(2H, d, J=6.4Hz), 8.50(1H, s)
252	Ex 3	H		Bn	F: 389
253	Ex 3	H		Bn	F: 389 ; NMR1: 2.28(3H, s), 4.70(2H, d, J=6.3Hz), 8.55(1H, s)
254	Ex 3	H		Bn	F: 375 ; NMR1: 3.14-3.18(2H, m), 4.66(2H, d, J=5.9Hz), 8.49 (1H, s)
255	Ex 3	H		Bn	F: 375
256	Ex 3	H		Bn	F: 389
257	Ex 3	H		Bn	F: 373
258	Ex 3	H		Bn	F: 403 ; NMR1: 2.11(3H, s), 4.69 (2H, d, J=5.9Hz), 8.55(1H, s)
259	Pre 15	H		Bn	F: 371
260	Pre 15	H		Bn	F: 359
261	Pre 15	H		Bn	F: 360
262	Pre 15	H		Bn	F: 360
263	Pre 15	H		Bn	F: 378

(Table 20 continued)

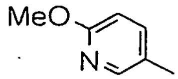
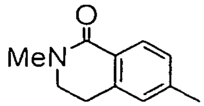
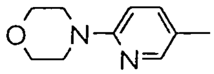
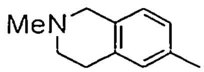
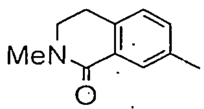
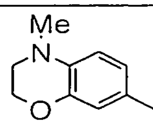
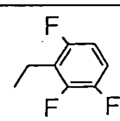
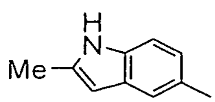
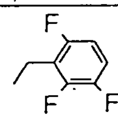
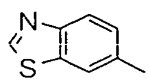
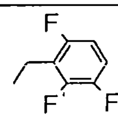
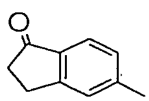
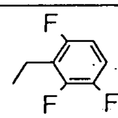
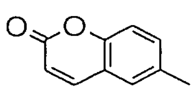
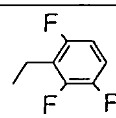
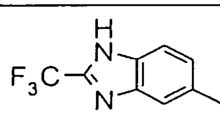
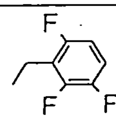
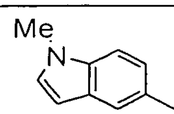
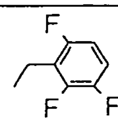
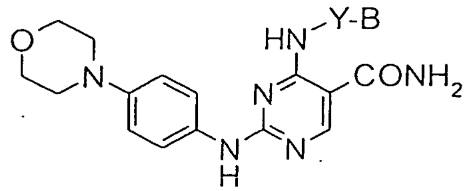
264	Pre 15	H		Bn	F: 351
265	Ex 3	H		Bn	F: 403 ; NMR1: 2.99(3H, s),4.76 (2H, d, J=5.8Hz), 8.63(1H, s) Sal: 2HCl
266	Ex 3	H		Bn	F: 406 Sal: 2HCl
267	Ex 3	H		Bn	F: 389 ; NMR1: 2.97(3H, s),4.73 (2H, d, J=5.9Hz), 8.63(1H, s) Sal: 2HCl
268	Ex 3	H		Bn	F: 403 Sal: HCl
269	Ex 3	H			F: 445 ; NMR1: 2.84(3H, s),4.86 (2H, d, J=5.9Hz), 8.59(1H, s) Sal: HCl
270	Pre 15	H			ESI: 427
271	Pre 15	H			ESI: 431
272	Pre 15	H			ESI: 428
273	Pre 15	H			ESI: 442
274	Pre 15	H			ESI: 482
275	Pre 15	H			ESI: 427

Table 21



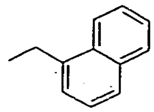
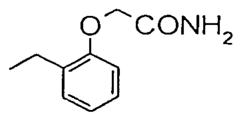
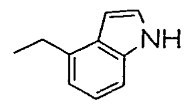
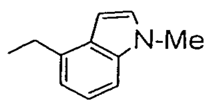
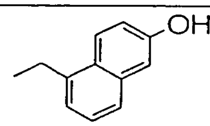
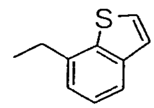
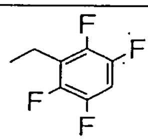
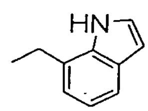
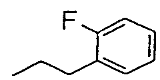
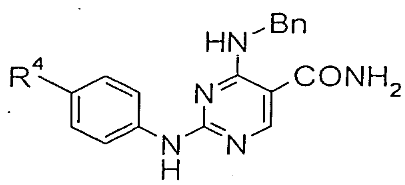
Cmpd	-Y-B	Cmpd	-Y-B	Cmpd	-Y-B
1		4		7	
2		5		8	
3		6		9	

Table 22



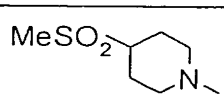
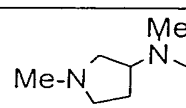
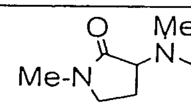
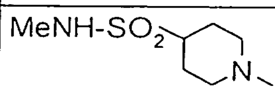
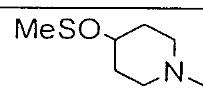
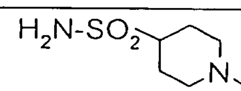
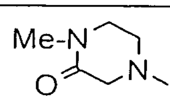
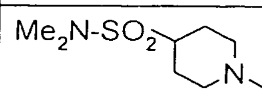
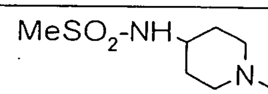
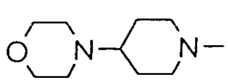
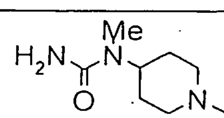
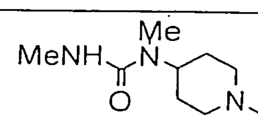
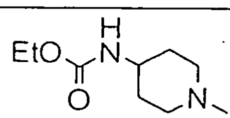
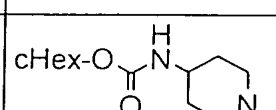
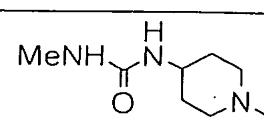
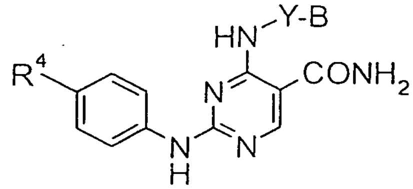
Cmpd	R^4	Cmpd	R^4	Cmpd	R^4
10		15		20	
11		16		21	
12		17		22	
13		18		23	
14		19		24	

Table 23



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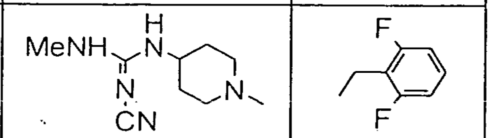
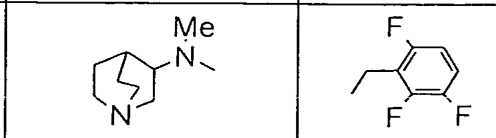
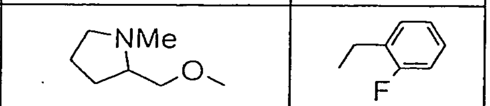
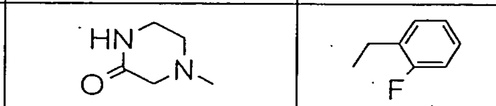
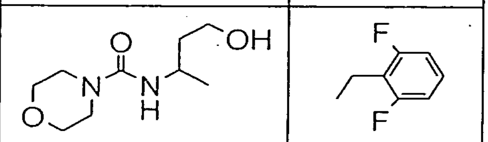
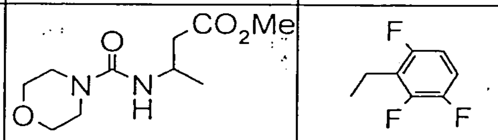
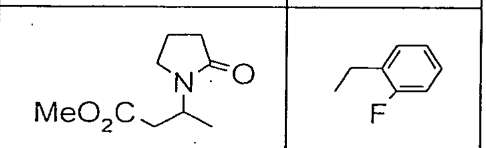
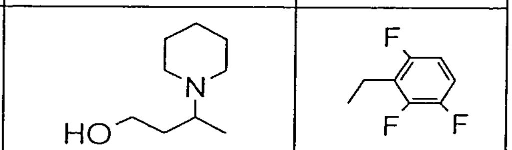
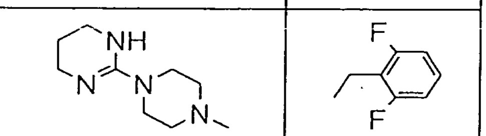
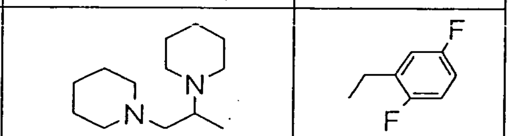
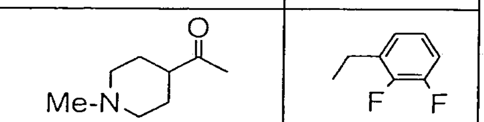
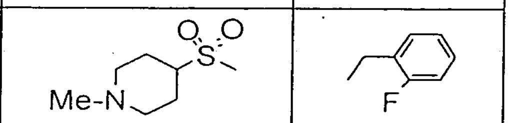
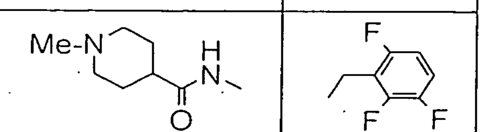
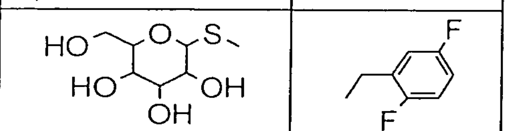
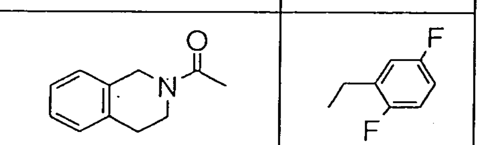
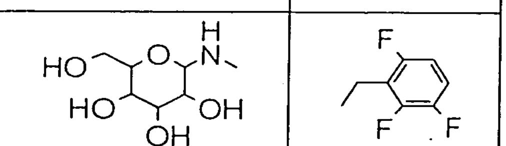
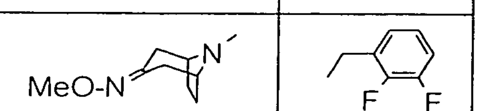
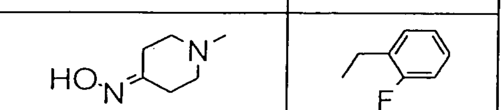
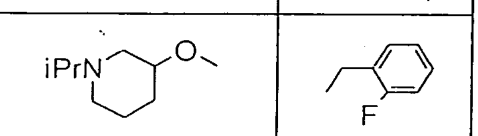
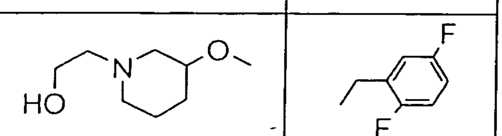
25			35		
26			36		
27			37		
28			38		
29			39		
30			40		
31			41		
32			42		
33			43		
34			44		

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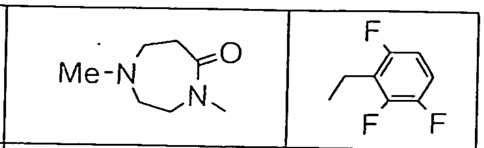
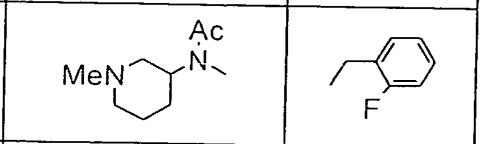
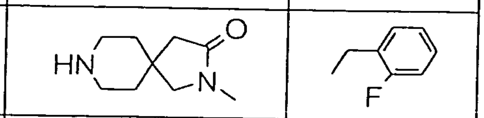
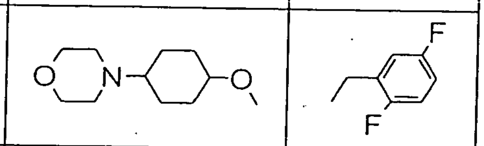
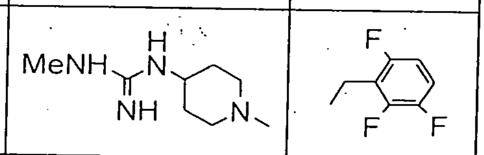
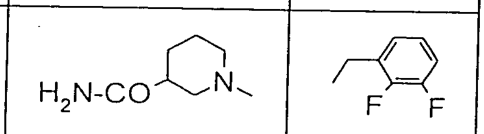
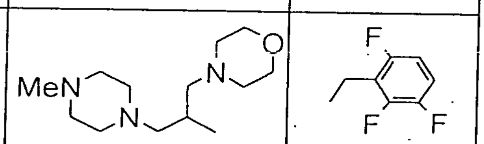
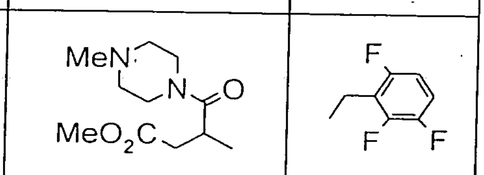
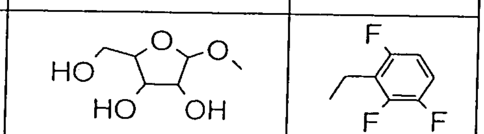
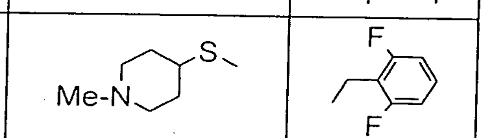
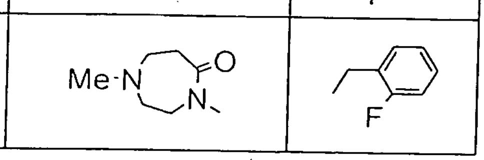
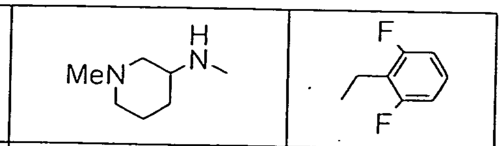
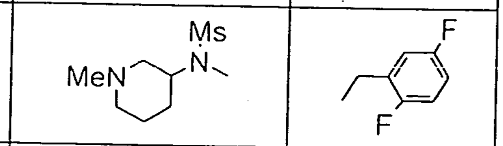
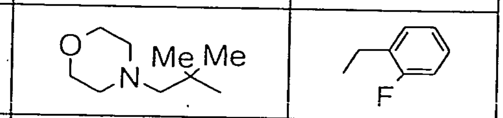
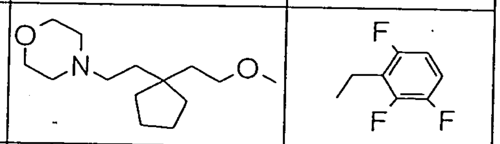
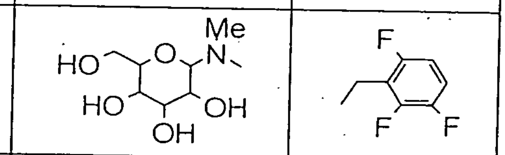
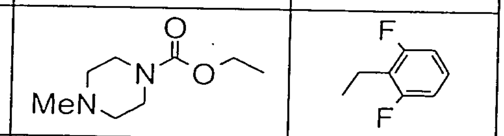
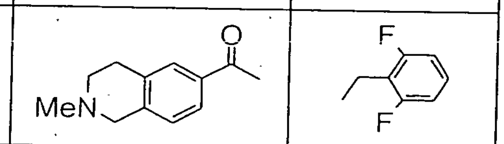
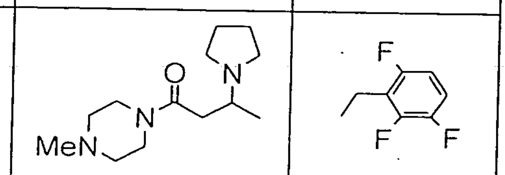
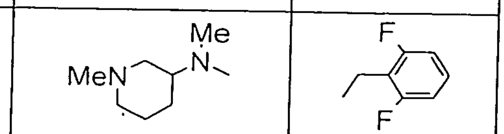
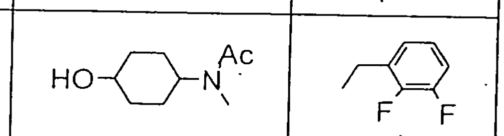
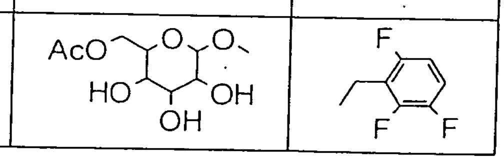
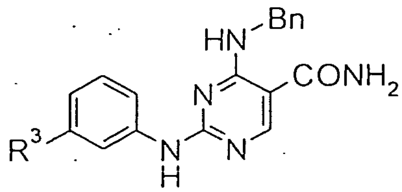
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	
61	
62	
63	
64	
65	
66	

Table 24



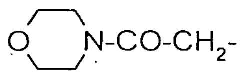
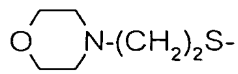
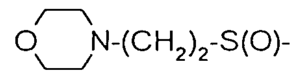
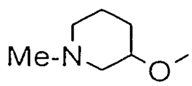
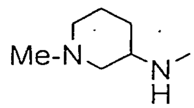
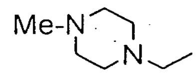
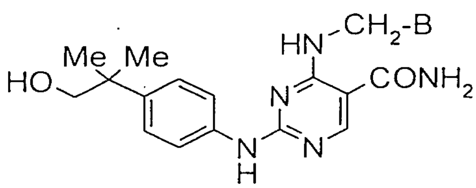
Cmpd	R^3	Cmpd	R^3	Cmpd	R^3
67		68		69	
70		71		72	

Table 25



Cmpd	B
73	2-F-Ph
74	2,5-F_2-Ph
75	3,5-F_2-Ph
76	2,6-F_2-Ph

Example 259 Measurement of STAT 6-dependent reporter activity

1) Construction of STAT 6 reactive reporter plasmid

A STAT 6 reporter plasmid pGL2-CI was prepared by the following method. Synthetic DNA molecules (SEQ ID NOs:1 and 2) containing a C/EBP binding sequence contained in the germline ε promoter sequence and an IL-4 reactive sequence in tandem were annealed and inserted into *Xho*I and *Bgl*II sites of pGL2-Basic vector (Promega). Also, DATA box sequence DNA molecules (SEQ ID NOs:3 and 4) contained in the adenovirus major late promoter were annealed and inserted into *Bgl*II and *Hin*dIII sites of the same vector. Thereafter, pGL2-CI/bs was constructed by inserting the blasticidin resistance gene of pUCSV-BSD (Funakoshi) into *Bam*HI site of the constructed pGL2-CI.

2) Construction of STAT 6 reporter cell

Gene transfer of pGV-CI/bs into a human IL-4 reactive cell FW4 cell (*Mol. Cell. Biol.*, 14: 5433 - 5440) was carried out by the electroporation method (320 V, 960 μF/0.4 cm cuvette (Nippon Bio-Rad Laboratories)), and 6 μg/ml of blasticidin (Funakoshi) was added 40 hours thereafter to select a resistant cell. Confirmation of constant transfer of the reporter plasmid was carried out by detecting luciferase induce by IL-4 stimulation. An STAT 6 reporter cell CI/FW4 was constructed by the above operation.

3) STAT reporter assay using CI/FW4 cell

Stimulation of the CI/FW4 cell (1 x 10^4 cells/0.1 ml) with 10 ng/ml of human IL-4 (Genzyme Techne) was carried out using a white 96 well plate (Nunc). In the case of the evaluation of compounds, compound dilutions were added to the wells before inoculating the cells into the 96 well plate. Also, regarding the dilution of compounds, dilution was carried out using 10% FBS-containing RPMI 1640 such that the final concentration of DMSO in which each compound was dissolved became 0.1% or less. A 50 μl portion of a cell lysis buffer (10 mM Tris-HCl pH 7.8, 0.5 mM $MgCl_2$, 10 mM dithiothreitol and 0.1% (v/v) Triton X-100) was added 16 hours after the IL-4 stimulation, followed by stirring for 1 minute. Thereafter, 50 μl of a luciferase substrate solution (10 mM Tris-HCl pH 7.8, 5 mM luciferin, 2 mM coenzyme A, 2 mM ATP, 0.5 mM $MgCl_2$ and 2 mM $Mg(OH)_2$) was added, followed by stirring for 1 minute. Then, the luciferase activity was measured using ML3000 luminometer (Dynatech Laboratories, Inc). Inhibitory activities of tested compounds were evaluated in which the luminescence intensity (relative light unit: RLU) of measured value by ML3000 when DMSO was added instead of a compound was regarded as 100%, and the RLU when IL-4 stimulation was not carried out as 0%.

The results are shown in the following Table 26. Ex indicates Example compound number, Pre indicates Production

Example compound number, Inh indicates inhibition ratio when each compound is 1 μM or 0.1 μM, and NT indicates not tested. Also, ref 1 and ref 2 are compounds disclosed in WO 99/31073 as the most desirable compounds, and ref 1 is the compound described in Example 15 (2-(2-aminoethylamino)-4-(3-methylanilino)pyrimidine-5-carboxamide) and ref 2 is the compound described in Example 35 (2-(cis-2-aminocyclohexylamino)-4-(3-methylanilino)pyrimidine-5-carboxamide).

Table 26

Ex	Inh (%)	
	1 μM	0.1 μM
1	100	89
2	96	48
3	100	100
35	100	95
37	100	100
38	100	100
39	100	100
62	100	99
63	100	100
64	100	100
125	100	100
127	100	96
128	100	94

Ex	Inh (%)	
	1 μM	0.1 μM
148	100	94
180	100	91
189	100	100
190	100	100
191	100	100
192	100	100
193	10	100
201	100	100
209	100	100
233	100	25
244	100	97
258	100	98

Pre	Inh (%)	
	1 μM	0.1 μM
1	100	67
9	91	33
12	100	91
127	100	60
178	100	69
253	100	94
269	100	96
ref 1	19	NT
ref 1	0	NT

In addition, the Example and Production Example compounds shown below also showed good activity similar to the compounds shown in the above Table 26: Examples 16, 43, 48, 58, 60, 72, 84, 96, 98, 117, 239 and 249, and Production Examples 99, 109, 204 and 265.

Example 260 Measurement of STAT 6 tyrosine phosphorylation

The H292 cell (ATCC) (5×10^5 cells/0.5 ml) was inoculated into a 12 well plate (IWAKI) and cultured overnight, and then stimulation with 10 ng/ml of human IL-4 (Genzyme techne) was carried out. In the case of the evaluation of compounds, compound dilutions were added to the wells 20 minutes before the IL-4 stimulation. Also, regarding the dilution of compounds, dilution was carried out using 10% FBS-containing RPMI 1640 such that the final concentration of DMSO in which each compound was dissolved became 0.1% or less. This was washed three times with ice-cooled physiological phosphate buffer 20 minutes after the IL-4 stimulation. After the washing, 100 μl/well of a cell lysis solution (TNE buffer: 10 mM Tris-HCl pH 7.8, 1% NP-40, 0.15 M NaCl, 1 mM EDTA, 10 μg/ml aprotinin, 1 mM NaF and 1 mM Na_3VO_4) was added. The cell lysate was recovered, and 15 μl thereof was subjected to western blotting after SDS electrophoresis using an anti-tyrosine phosphorylated STAT 6 antibody (Cell Signaling). Whether or not the tyrosine phosphorylation band of about 110 kDa is disappered, which is IL-4 stimulation-dependently detected, was judged. Also, uniform transference of the STAT 6 protein was confirmed using the same transfer membrane by western blotting which used an anti-STAT 6 antibody (SantaCruz).

As a result of the above test, it was confirmed that tyrosine phosphorylation was inhibited by the compounds of the present invention. For example, it was completely inhibited by 1 μM of the compounds of Examples 3, 37, 35, 60, 72, 84, 96, 98, 148, 189, 190, 191, 192, 193, 201, 209 and 249 and Production Examples 99, 265 and 269.

Example 261 Measurement of Th2 differentiation

T cells were prepared by removing nylon wool (Wako Pure Chemical Industries)-adhering cells from C57BL/6 mouse (Charles River Japan) spleen cells. Using a 96 well plate to which an anti-CD3 ε antibody (10 μg/ml) (Sederlane) had been immobilized in advance, T cells (2 x 10^5 cells/0.2 ml) were inoculated under stimulation with anti-CD28 antibody (1 μg/ml) (Pharmingen), IL-2 (10 ng/ml) (Peprotech) and IL-4 (10 ng/ml) (Peprotech). After 2 days of the culturing, total volume of the cell suspension was diluted to 2 ml with a medium containing IL-2 (10 ng/ml) and IL-4 (10 ng/ml). The differentiation was induced by further carrying out the culturing for 3 days. By counting the cell density, the cells after differentiation were adjusted to 1 x 10^6 cells/ml and inoculated into a 96 well plate immobilized with the anti-CD3 ε antibody, in order to induce IL-4 production. The supernatant after 24 hours of the stimulation was recovered, and the IL-4 production was determined by an ELISA method. The antibody used in the

ELISA was purchased from Pharmingen. Also, an HRPO-labeled streptoavidin (Amersham Pharmacia) was used in the detection of biotinylated antibody, and a peroxidase color developing reagent (Sumitomo Bakelite) was used in the HRPO color development. In the case of the evaluation of compounds, compound dilutions were added to the wells before the addition of T cells, at the time of the dilution 2 days later, compounds equivalent to the initial concentration were added. Also, regarding the dilution of compounds, dilution was carried out using 10% FBS-containing RPMI 1640 such that the final concentration of DMSO in which each compound was dissolved became 0.1% or less. Inhibitory activity of each tested compound was evaluated in which the IL-4 production when DMSO was added instead of the compound was regarded as 100%, and the IL-4 production when anti-CD28 antibody and IL-4 were not added as 0%. The inhibition ratio of each tested compound at a concentration of 10 nM is shown in the following Table 27.

Table 27

Ex	Inh (%)
1	88
3	98
16	82
35	94
37	93

Ex	Inh (%)
48	92
60	99
63	96
64	93
117	85

Pre	Inh (%)
99	85

ref 1	0
ref 2	0

Example 262 Evaluation using mouse asthma model

Active sensitization of female Balb/c mice were carried out by intraperitoneally administering ovalbumin (OA) and an adjuvant, aluminum hydroxide gel (alum), twice. Mice were exposed to OA by inhalation 12 days after the initial sensitization and sacrificed by bloodletting 72 hours after the exposure, and then alveolar lavage was carried out. A compound to be tested or a control, 0.5% methyl cellulose, was orally administered for 3 days from before the OA exposure to before the alveolar lavage. After the measurement of total white blood cell count in the alveolar lavage fluid, cell smear preparations were stained to calculate existing ratio of eosinophil based on its morphological characteristics. The total number of eosinophils was calculated from the total white blood cell count and existing ratio of respective kinds of cells. As a result, hydrochloride of the compound of Example 3 inhibited about 60% of the antigen-induced eosinophil infiltration by its oral administration at a dose of 1 mg/kg.

Example 263 Evaluation using SO_2 gas-induced intra-alveolar neutrophil infiltration model mouse asthma model

Male C57BL/6 mice were exposed to SO_2 gas (600 ppm) for 3 hours and sacrificed by bloodletting 48 hours after the exposure, and then alveolar lavage was carried out.

After the measurement of total white blood cell count in the alveolar lavage fluid, cell smear preparations were stained to calculate existing ratio of neutrophil based on its morphological characteristics. The number of neutrophils was calculated from the total white blood cell count and existing ratio of respective cells. A compound to be tested or a control, 0.5% methyl cellulose, was orally administered for 2 days from just before the exposure or just after the exposure to before the alveolar lavage. As a result, hydrochloride of the compound of Example 3 inhibited about 70% of the neutrophil infiltration by its oral administration at a dose of 10 mg/kg.

Example 264 Evaluation using tobacco- and ozone-induced intra-alveolar neutrophil infiltration model

Male B6C3F1 mice were exposed to 3% tobacco smoke 3 hours per day for 3 consecutive days, from the 1st day to the 3rd day. On the 4th day, they were exposed to 0.5 ppm of ozone for 6 hours and sacrificed by bloodletting on the 5th day, and then alveolar lavage was carried out. After the measurement of total white blood cell count in the alveolar lavage fluid, cell smear preparations were stained to calculate existing ratio of neutrophil based on its morphological characteristics. The total number of neutrophils was calculated from the total white blood cell

count and existing ratio of respective cells. A compound to be tested or a control, 0.5% methyl cellulose, was administered just before the tobacco exposure or after completion of its exposure and before the ozone exposure.

It is evident that the compounds useful as the active ingredients of the present invention have excellent inhibitory activities for STAT 6 activation and Th2 differentiation from the results of the aforementioned Examples 259 to 261, and that they are useful as preventive or therapeutic agents for respiratory diseases and the like in which STAT 6 is concerned, such as asthma, COPD and the like from the results of the Examples 262 to 264.